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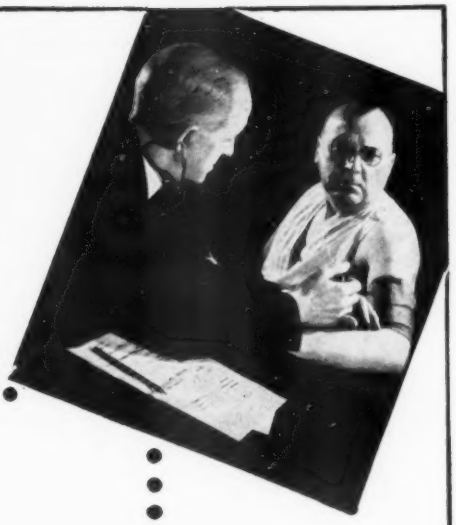

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

FEBRUARY, 1949

ORIGINAL ARTICLES

AN EPIDEMIC WAVE OF THYROTOXICOSIS IN DENMARK DURING WORLD WAR II.

By Kurt Iversen, M. D.,
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During world war II a peculiar rise in the frequency of thyrotoxicosis was observed in Denmark under the German occupation in 1941 to 1945. The rise began in 1941, all over the country, and reached its maximum in 1944. A preliminary report of this phenomenon was given in 1943 by *Meulengracht*[4], who described the rise in the occurrence of thyrotoxicosis on the basis of cases admitted to his own department (Dept. B., Bispebjerg Hospital, Copenhagen). Now, in 1948, the pre-war level has again been reached. The rise was abrupt and high, of transitory or, so to speak, of "epidemic" character and its cause was so obscure, that it seemed worth analyzing in detail.

A question of particular interest for the present work is whether variations in the thyrotoxic morbidity have been seen before, especially during the war of 1914 to 1918. On this point, opinions are rather divergent. Still, a number of fairly well substantiated reports are available, showing that in Germany and Finland the incidence of thyrotoxicosis decreased considerably during the war of 1914-1918 and in the first years thereafter. Further, a rise in the frequency of thyrotoxicosis like the one observed here in Denmark has been recorded only once before, namely: in Olmstead County, Minnesota, during the years 1924 to 1927. This "epidemic" rise has been described by *Plummer*[5] who states, however, that the data on which the assumption of the rise is based are somewhat defective. Thus he had no chance of ascertaining how large a percentage of the thyrotoxic patients in the Northwest and Great Lakes' region were admitted to the Mayo Clinic. On the basis of the available data Plummer would not venture to say anything about the cause of the "epidemic". After all, to me it seems more reasonable to assume that the phenomenon in question is a result of extraordinary conditions in connection with the Plummer treatment of thyrotoxicosis with iodine, which started just some years before, and thus the rise is not to be taken as a real increase in the morbidity, but rather attributable to a change in the general hospitalization of patients.

The Danish "Epidemic". In order to get an idea about the frequency of thyrotoxicosis in Denmark through a number of years, I have gone through the annual reports from all the hos-

pitals in this country within the period of 1931 to 1945. For several reasons, however, the numerical data obtained in this way are inaccurate, giving by no means the absolute occurrence of thyrotoxicosis in Denmark.

For one thing, it has to be realized that hardly all cases of this kind are hospitalized. Further, in making use of the annual reports from the hospitals it is not practicable to rule out all readmissions; besides, the same patient may be registered twice in the same annual report, under the medical as well as surgical departments.

In Fig. 1 all the hospitalized cases of thyrotoxicosis in Denmark, *according to the annual reports*, are recorded graphically. From this it is evident that since 1931 there was a gradual and continuous rise in the frequency of thyrotoxicosis until 1941, when a sudden rise set in that continued also in the following 2 years. Thus in 1943 the number of cases was 3 to 4 times higher than in the years before the

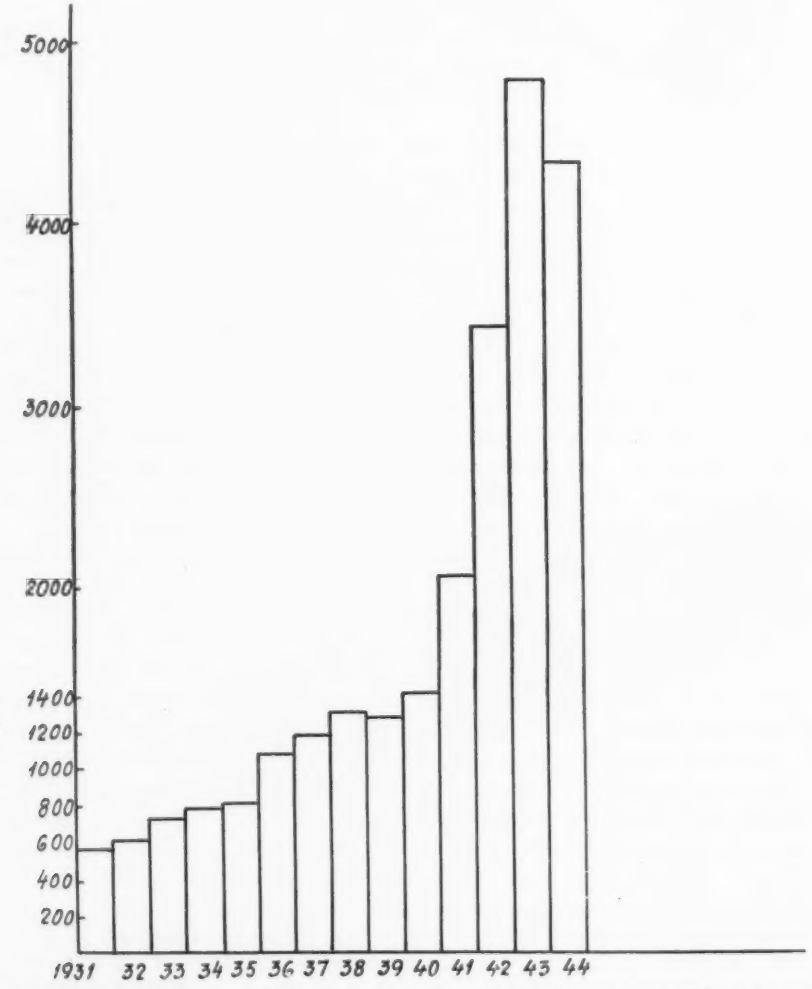

FIG. 1.—All hospitalized cases of thyrotoxicosis in Denmark in the period of 1931 - 44, according to the annual reports from the hospitals.

war. The rise had culminated in 1944, when the incidence commenced to fall, and this fall continued in 1945.

A detailed analysis showed that the sudden rise in thyrotoxicosis in 1942 was distributed equally over all the counties of the country. It commenced at the same time all over the country and was of almost the same magnitude in the various counties.

For reasons already mentioned the annual reports are not serviceable for an accurate estimate of the occurrence of thyrotoxicosis. This requires an individual registration of each case so as to exclude readmissions and relapses. Besides, this is the only way in which all dubious cases may be ruled out. In order to keep this task within reasonable limits I have chosen to investigate the occurrence of thyrotoxicosis within the municipality of Copenhagen. The rise in the incidence of the disease has been just as pronounced here as in the entire country and the material may be said to be representative for such investigation.

Material. The present material comprises *all newly-diagnosed hospitalized cases of thyrotoxicosis residing in the municipality of Copenhagen within the period of 1938 to 1947.*

No absolutely accurate figure for the occurrence of the disease in the popu-

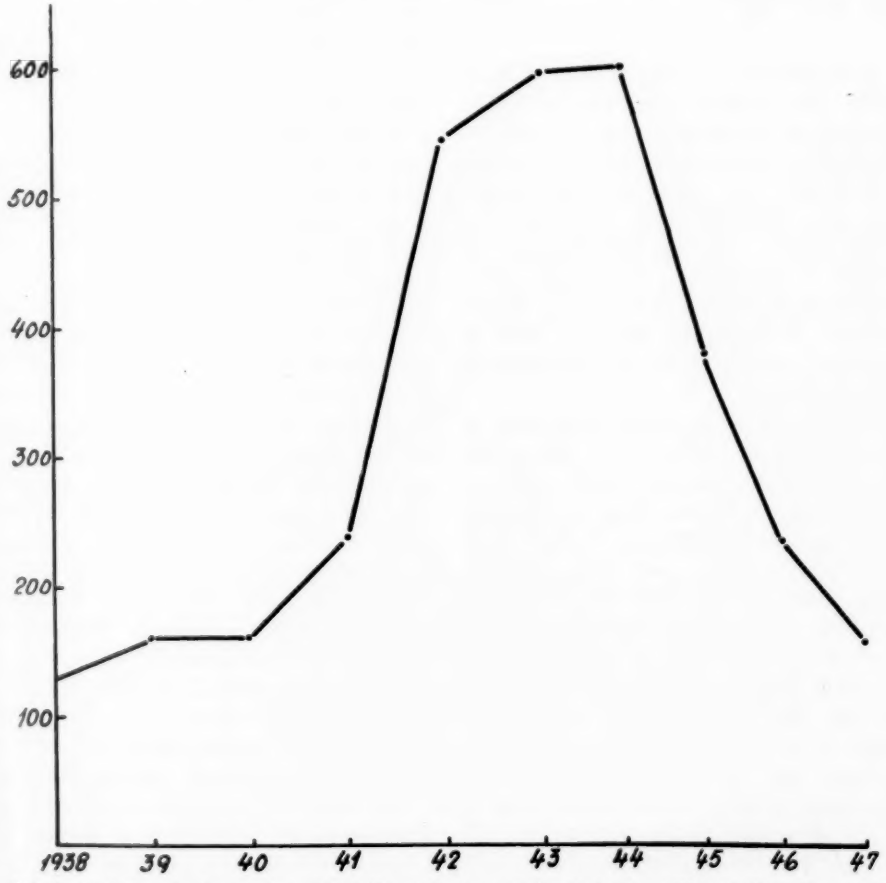

FIG. 2.—Variations in the number of first-diagnosed cases of thyrotoxicosis residing in Copenhagen and admitted to Copenhagen hospitals in 1938-47 (in absolute figures).

lation may be obtained in this way, it is true, but I feel convinced that only an insignificant number of patients here in Copenhagen have not been hospitalized at some juncture of their illness. This has further been confirmed privately by several practising physicians in Copenhagen.

TABLE 1.—SHIFT IN THE MORBIDITY OF THYROTOXICOSIS FOR THE CITY OF COPENHAGEN IN 1938 TO 1947

	No. of cases	No. of inhabitants	No. of cases in %
1938	129	687625	0,19
1939	159	691995	0,23
1940	160	700465	0,23
1941	240	702424	0,34
1942	546	711224	0,77
1943	598	714589	0,84
1944	591	724071	0 83
1945	379	731707	0,52
1946	235	753010	0,31
1947	157	759114	0,21

The material includes *a total of 3194 cases*. The *average incidence* of thyrotoxicosis in Copenhagen in this period is found to have been 0,44—pro mille.

In Table 1 the cases are recorded for each year together with the census for Copenhagen. In 1938 the disease occurred in 0,19‰ of the population, and in the following 4 to 5 years it increased so markedly that in 1943 it occurred in 0,84‰ of the inhabitants of Copenhagen.

In Fig. 2 this rise in the frequency is presented graphically. From this it will be noticed that the rise from 1938 to 1940 is fairly gradual, while it becomes more marked in 1941, and then in 1942 it is quite abrupt and keeps at the high level for the following 2 years. In 1944 this rise has culminated, and as early as 1945 there is a rather considerable fall in the number of cases. In 1947 the pre-war level is reached again.

From Fig. 1, which is plotted on the basis of the annual reports from all the hospitals in the country, it will be seen that the gradual rise from 1938 to 1940 practically is to be looked upon as a continuation of the steady increase since 1931. The cause of this gradual rise in this period seems most likely to be due to greater interest in the disease and a more ready recognition of it.

As for *the sudden rise in 1942*, it is hardly conceivable that it might be a simple continuation of a preceding gradual rise. *It is directly suggestive of some extraordinary underlying conditions.*

Before discussing the cause of this peculiar rise, we first have to realize that it is due to a real increase in the morbidity and not to some irrelevant factors. And it may be at once said that neither increase in the population nor any change in the tendency to hospitalization of the patients may give any adequate explanation of the phenomenon.

It also seems improbable that improved diagnosis might bring about such a sudden rise in the frequency of the disease. As already mentioned, the increase is distributed evenly all over the country. In other words, if improved diagnosis were the cause of the rise, it would mean that all physicians throughout the country in 1942 suddenly had acquired a much greater diagnostic capacity as far as the recognition of thyrotoxicosis is concerned. It would hardly be reasonable to assume this, particularly as the disease on the whole had become more severe. Moreover, the decreased frequency of thyrotoxicosis in 1945 most decidedly goes against such a possibility. Besides, if improved diagnosis really played any rôle here, we would expect that the practising physicians now referred more patients to the hospitals with a correct diagnosis than before. But, on going through the admitting diagnoses, year by year, no particular change is found in this respect. Conceivably the rise might have been due to increasing

employment of metabolism determination, so that more mild cases were detected now than before, but an enumeration of the employed determinations of metabolism showed the contrary.

Further, by dividing the material into mild and severe cases (with and without exophthalmus) it was evident (see Fig. 3) that the severe cases without exophthalmus showed the greatest increase, 7 to 8 times the number of cases in 1938; but also the severe cases with exophthalmus (that is, the classical type) had increased considerably (almost 5 times). The mild cases had increased least, even though their number had tripled since 1938. The fact that the rise in frequency is far more pronounced for the severe cases goes directly against its being due to improved diagnosis, provided that the clinical picture of the disease has not changed in character in the years concerned.

It was necessary therefore to investigate the symptomatology of the entire material and make a comparison between the cases from the first period (1938 to 1940) and the cases that appeared during the abrupt rise in 1942 to 1943.

A detailed analysis of the total material, which comprises altogether 1832

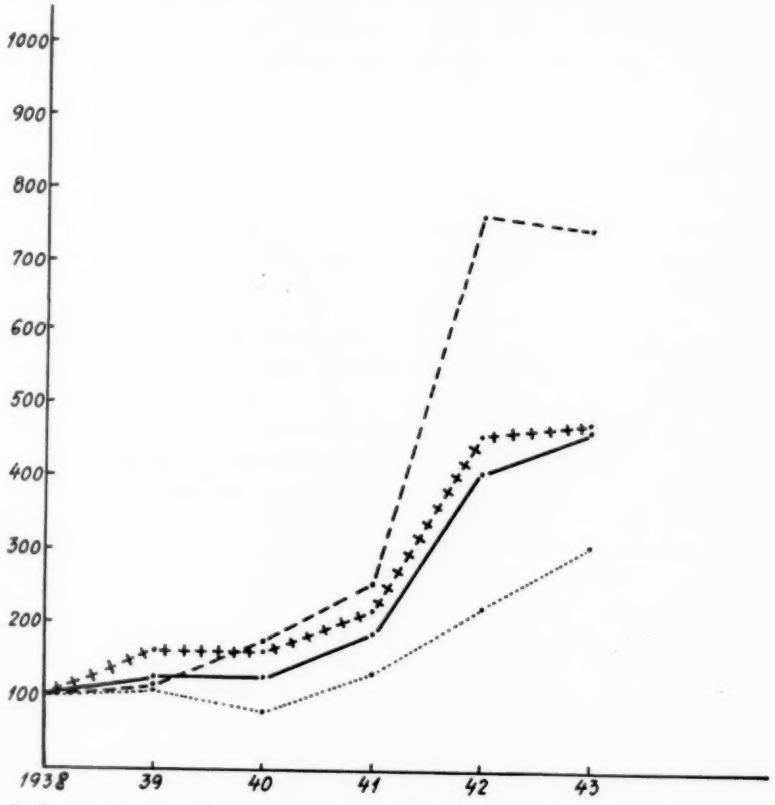

FIG. 3.—Rise in frequency of thyrotoxicosis for the three groups of cases, based on index values. (The number for 1938 set = 100.)

———: Entire material
– – – – –: Severe thyrotoxicosis without exophthalmus.
+++++: Severe thyrotoxicosis with exophthalmus.
.....: Mild thyrotoxicosis.

cases of new-diagnosed thyrotoxicosis, shows that *thyrotoxicosis in Denmark now appears in a more oligosymptomatic form than previously.*

It is especially the objective symptoms, however, that show the more distinct differences between the 2 groups. Thus, pronounced enlargement of the thyroid, exophthalmus and tachycardia occurred less frequently among the cases during the rise. Further, the determinations of the metabolism showed significantly higher values for the cases during the rise and correspondingly these patients also had greater loss in weight.

It is reasonable to assume that this change in the symptomatology primarily is attributable to a greater interest taken more recently in the forms of thyrotoxicosis and thus also to a better recognition of the variegated clinical manifestations of thyrotoxicosis.

The next question is whether these "masked" or oligosymptomatic cases of thyrotoxicosis seen during the rise of

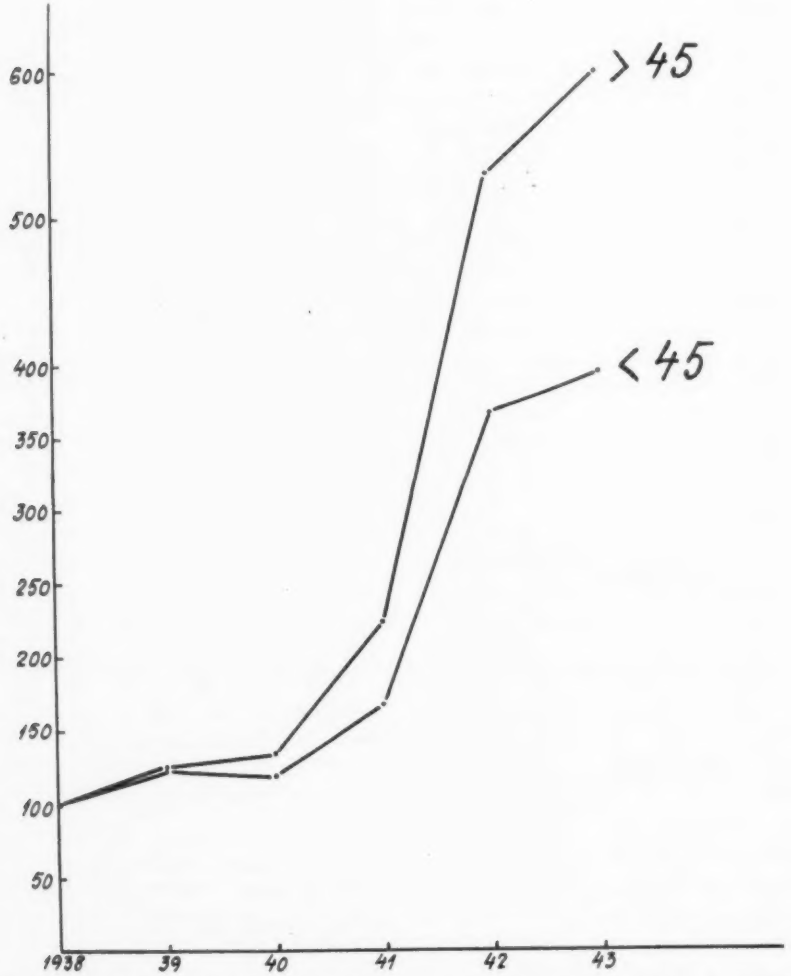

FIG. 4.—Rise in the number of thyrotoxic patients under and over 45 years, based on index values. (The number for 1938 set = 100.)

the disease may have increased to such an extent that the addition of these cases might explain the general rise in the frequency of thyrotoxicosis here in Denmark.

It proved impracticable, however, to obtain an accurate numerical expression for these cases through a retrospective investigation like this one. For it may always be questionable whether in a given case the lesion correctly has been looked upon as "masked", or whether its "masking" might not rather be due to failing diagnostic ability of the examiner. In material like the present, collected from many clinics, such a selection of masked cases could not avoid being rather arbitrary, on which account I had to give up my original plan to separate all masked cases of thyrotoxicosis in order to see whether they had increased to such an extent that the addition of these cases might explain the general rise in the frequency of thyrotoxicosis.

If improved diagnosis had played any rôle in the rise in frequency, we would expect the rise to involve exclusively—or at any rate chiefly—the older patients, as the symptoms are relatively more scanty in the higher age-classes. In Fig. 4 we see the rise in frequency for patients over 45 years compared with the rise for patients under 45. The curves here are plotted on the basis of index values, the values for 1938 set =100. The rise is found to be greater for patients over 45 years: 6 times their initial number. But the rise is also quite considerable for patients under 45 years, their number being quadrupled. In other words, this means that even the younger thyrotoxic patients—with nearly the same form of clinical manifestation of their illness—have increased considerably in number during these years.

To me these findings seem to indicate *that the rise in the frequency of thyrotoxicosis in Denmark must chiefly be due to a real increase in morbidity even though improved diagnosis possibly may explain a part of it.*

Variations in the Frequency of Thyrotoxicosis in Countries Other than Denmark during World War II. In an investigation like the present it is of great interest to establish whether a sudden rise in the occurrence of thyrotoxicosis similar to the one observed in Denmark during the last war may have taken place at some point of time in other countries. On going through the *mortality statistics* from various countries (Norway, Sweden, Great Britain, Canada, United States, New Zealand and Holland), covering the last 40 years, it is found that since 1910 there has been a gradual, though rather considerable, rise in the thyrotoxicosis mortality. But a sudden or abrupt rise like that just observed in Denmark has not been seen before.

More recent reports from other countries indicate that *during world war II there was a distinct decrease in the frequency of thyrotoxicosis in Holland* (*Schweitzer*[6]) *and Belgium* (*Bastenie*[1]). The respective authors have been most inclined to associate this fact with the general malnutrition of the Dutch and Belgian population.

In *Norway*, during the beginning of the German occupation, in 1941 there was a distinct rise in the frequency of thyrotoxicosis, but already, in the following year, simultaneously with the nutritional crisis, there was a noticeable decrease in the incidence of the disease that became more accentuated in the following years (*Grelland*[2]).

Through private questionnaires to a number of thyroid investigators in Europe and America, supplementary information has been obtained about the thyrotoxicosis morbidity during the war. From this it is evident that no *variations in the frequency of thyro-*

toxicosis was observed in Sweden, Finland, Great Britain, Switzerland, United States or Argentina. In Paris a considerable rise in the frequency of the disease also seems to have been observed, according to *Alison* (personal communication), but it seems to have been a localized phenomenon and not fully established.

So, while during the war and the German occupation the frequency of thyrotoxicosis rose considerably in Denmark, there was a marked fall in the incidence of the disease in Holland and Belgium, and in Norway there was a minor rise in the first year of occupation, followed by a distinct fall.

As a matter of fact, we might say that in the countries during the war a human experiment was taking place on a very large scale.

Possible causes of the temporary rise in frequency of thyrotoxicosis. One factor common to the 4 countries was *the hard psychic strain* to which the population was submitted; and yet the frequency of the disease differed in these countries. While in Denmark the diet in general was adequate qualitatively as well as quantitatively throughout the war, there was a considerable degree of malnutrition in the other countries, and in Norway this did not become particularly pronounced till 1942 and 1943 when the frequency of the disease fell off markedly.

At first glance these findings may be taken to indicate that psychic strain has not played any particular rôle, whereas the nutritional conditions may be assumed to have played a considerable part in the difference in the frequency of thyrotoxicosis in the countries concerned.

It must be said to be most dubious whether a psychic trauma might bring about or elicit a state of thyrotoxicosis. In the writer's material, positive data on previous psychic trauma were available only in 5% of the cases; and only in 2/5 of these patients was the interval between the psychic trauma and the first manifestation of the disease less than 3 months. This suggests that a psychic trauma cannot play any great rôle in the etiology of thyrotoxicosis on the whole.

Naturally it would be of particular interest to clear up the question whether the rise in the frequency of thyrotoxicosis in Denmark in recent years possibly might have been due to the heavy psychic strain to which the Danish population was exposed under the German occupation.

As to this point, it may be said that the psychic strain from the German occupation asserted itself more forcibly in 1944 and 1945, when the German terrorism with "clearing murder", etc., became more atrocious than before, whereas the rise in thyrotoxic morbidity had already commenced in 1941.

No evidence is found that would permit us to assign any particular etiological rôle to any *known infectious diseases* as far as the development of thyrotoxicosis is concerned. Nor has any evidence been found in support of the assumption that thyrotoxic patients would be more liable than other persons to catarrhal infections of the air passages. But it must be admitted that the demonstrated curve (Fig. 2) of the temporary rise in the frequency of thyrotoxicosis in Denmark has some resemblance to a typical epidemic curve.

Previously some experimental studies have been published, showing that exposure to cold gives rise to certain histological changes in the thyroid, indicating hyperactivity of the gland. These changes greatly resemble the picture encountered after administration of thyrotropic hormone.

In this connection attention may be called to the fact *that 3 extraordinarily cold winters occurred immediately be-*

fore and simultaneous with the rise in the frequency of thyrotoxicosis in Denmark. The same appears to have applied also to the wave of the disease in Minnesota in the years of 1924 to 1926 according to the annual meteorological reports. But, whether these extraordinary climatic conditions may have been connected with the rise in thyrotoxicosis cannot be decided with certainty.

The idea that the rise in the frequency of thyrotoxicosis in Denmark during the war may have been associated with *certain changes in the nutrition,* may be said to seem rather obvious. A fairly thorough analysis of the dietary conditions during this period, however, shows that only relatively slight changes have taken place. Thus, for instance, the caloric consumption was lowered from 3071 to 2687 calories per individual from 1939 to 1945. There has been a minor increase in the protein consumption, while the consumption of fat and carbohydrate has been decreasing. The "protective food" content of the diet has rather been increasing. An analysis of the diet of this sort cannot give any explanation of the cause of the peculiar rise in the frequency of thyrotoxicosis in these years.

Perhaps changes in the content of some antithyroid factors of the diet may give a plausible explanation as to the origin of the "epidemic wave" of thyrotoxicosis in Denmark during the war, even though nothing definite can yet be said about it. For further details concerning this discussion, the reader may be referred to a monograph by the writer[3].

Summary. A description and analysis have been given of a peculiar and temporary rise in the frequency of thyrotoxicosis in Denmark during World War II. The rise set in suddenly in 1941 and reached its peak in 1944. In 1947 the pre-war level was again reached. It is shown that the rise in the frequency of the disease in these years must be due to a real increase in morbidity. The causes of the phenomenon has been discussed briefly, but no definite and adequate explanation of this peculiar "epidemic wave" of thyrotoxicosis may yet be offered.

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EXPERIMENTAL STUDY OF LIFE SITUATIONS, EMOTIONS, AND THE OCCURRENCE OF ACIDOSIS IN A JUVENILE DIABETIC.

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It is known that the regulation of diabetes mellitus becomes more difficult when the patient is under stress from infection or trauma, or during periods of emotional conflict. "Emotional glycosuria" has been demonstrated both in man and in experimental animals.[1,4,6] There has been reported the occurrence of diabetes in a setting of emotional conflict, and furthermore, fluctuations in the disorder have been correlated with the emotional state in some patients.[2,3,5,7,8,9] In the study here reported, the relation between ketonuria, life situation, and emotional state has been investigated.

Case Report: The patient was a 15 year old schoolgirl who had been admitted to the New York Hospital 13 times in diabetic acidosis. Two of these episodes of acidosis had been attributed to intercurrent infection, but the remainder were unexplained. It was generally felt that they had been precipitated by the patient's wilful neglect to take insulin and to follow her diet.

The girl was the youngest of 5 children of a Roman Catholic laborer and his wife. The father was a mild and ineffectual man, while the mother was an anxious, hypochondriacal woman who was the tyrant of the family. She exhibited mixed feelings of resentment and guilt toward the patient, who was an unplanned and unwanted child 7 years younger than her next older sibling. The mother's behavior toward the girl, consisted of extremely restrictive discipline accompanied by towering rages in which she often beat her, alternating with periods of remorse and solicitude.

There was no family history of diabetes.

The patient showed no abnormalities of birth or physical development, and, until the onset of her diabetes at age 11, she had no illness except the usual childhood diseases and an appendectomy for acute appendicitis. At a very early age, however, she showed rebellious feelings toward her mother's restrictions, as well as terror at the beatings which she received. It is not clear whether or not there were any important changes in her life situation at the time of onset of her diabetes. No evidence of such a change was elicited in numerous interviews. When the diagnosis of diabetes was made the mother was afraid of its implications, and doubled her restrictions upon the child.

At the time the patient was first seen at this hospital she was sullen and rebellious, but the general impression was that she was a child of superior intelligence (I. Q. 117) who had reacted characteristically to a frightening diagnosis. Although she was obese she showed no other physical abnormalities. During the following 4 years the conflict between her and her mother increased in intensity, and she developed repeated episodes of acidosis.

She was studied by the authors at the time of her 14th admission to the hospital. She was again found to be resentful and inwardly rebellious toward her mother. She was also extremely dependent upon her mother, passive, and unable to solve her dilemmas by positive action. It appeared that the mother's capricious tyranny had reduced the patient to a state of complete helplessness. She seemed either consciously or unconsciously to provoke many of the storms which descended upon her. She admitted that she ate indiscriminately and she stated that she often stopped her insulin because she "wanted to die." She always maintained, however, that her episodes of acidosis had begun to develop *before* she quit taking her insulin. Since her history suggested that a violent altercation with her mother usually preceded the appearance of

acidosis, it was decided to investigate the possible connection between these two events.

Detailed Study of the Occurrence of Acidosis: The patient was asked to keep a diary in which she recorded the happenings of the day, and expressed her attitudes and feelings toward them. Every two weeks she was seen in the clinic and the events of the fortnight were reviewed, with special attention to the circumstances surrounding the development of acidosis. No change was made in her insulin dosage, which previously had been elevated to 60 units of protamine insulin and 40 units of regular insulin in separate syringes before breakfast. Likewise, her diet was prescribed to include protein 80 gm., fat 60 gm., and carbohydrate 200 gm., limited to 1660 calories, because of her obesity. Three times a day, before meals, she examined her urine for sugar and acetone, and recorded the results in her diary. A hundred days of her life as gleaned from her diary are recorded in Figs. 1-5. There is no doubt that she took her insulin during this time. Her critical mother confirms this.

During the 1st week of the observation period the girl's life was relatively calm and uneventful. On the 8th day she decided to take a part-time volunteer job at the hospital—a decision which represented an act of unprecedented boldness and independence on her part. When she persisted in her decision despite the objections of her parents, she became anxious, "shaky," and fearful. After a

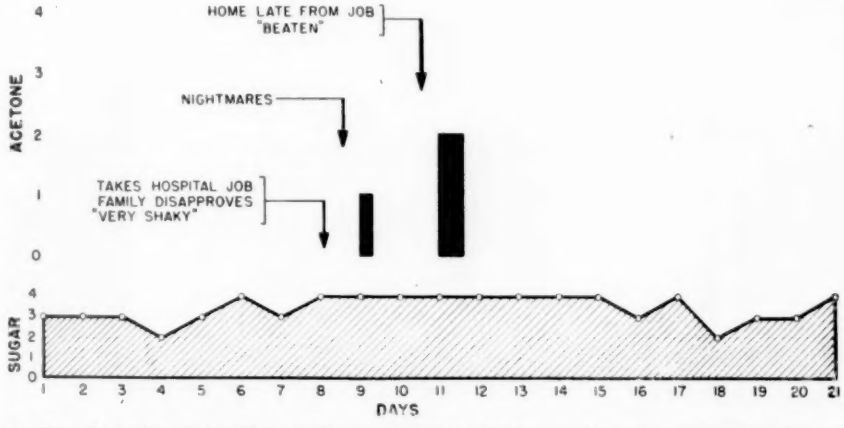

FIG. 1.—First 3 weeks of detailed correlation of urinary findings with events, attitudes and emotions.

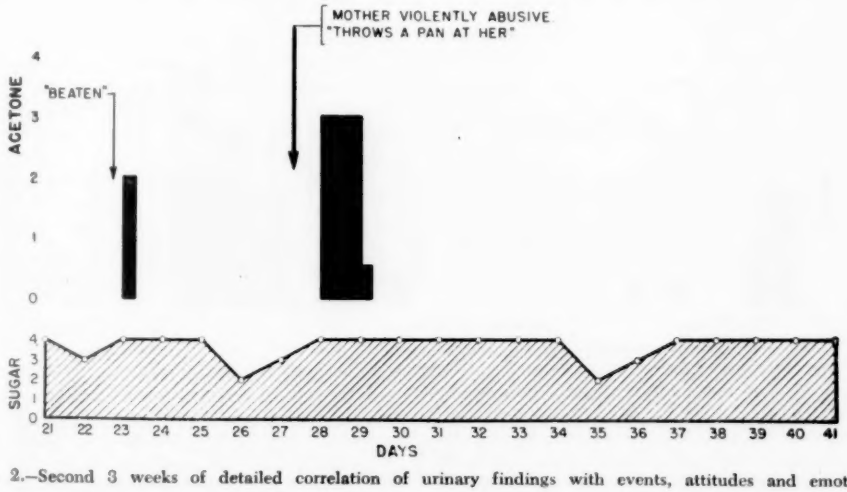

FIG. 2.—Second 3 weeks of detailed correlation of urinary findings with events, attitudes and emotions.

restless night punctuated by nightmares, she awoke on the 9th day to find acetone in her urine.

She was only partly reassured when the anticipated storm failed to materialize. On the 10th day she started work at the hospital. That night when she came home she found her mother violently angry. She was slapped with a dishrag and verbally abused for several hours. Although she became angry, she was also very much afraid. After another sleepless night she again found acetone in her urine.

Following this episode her mother was remorseful, and the patient became less apprehensive. A period of relative peace at home lasted until the 22nd day. Then an argument developed over apparently trivial matters. It was followed by a slapping. Again there was a sleepless night, and acetonuria appeared the next morning.

Several days later the mother, again feeling remorseful, bought her daughter a new dress; but shortly thereafter, on the 26th day, she once more became moody and threatening. On the 27th day the girl lost the belt

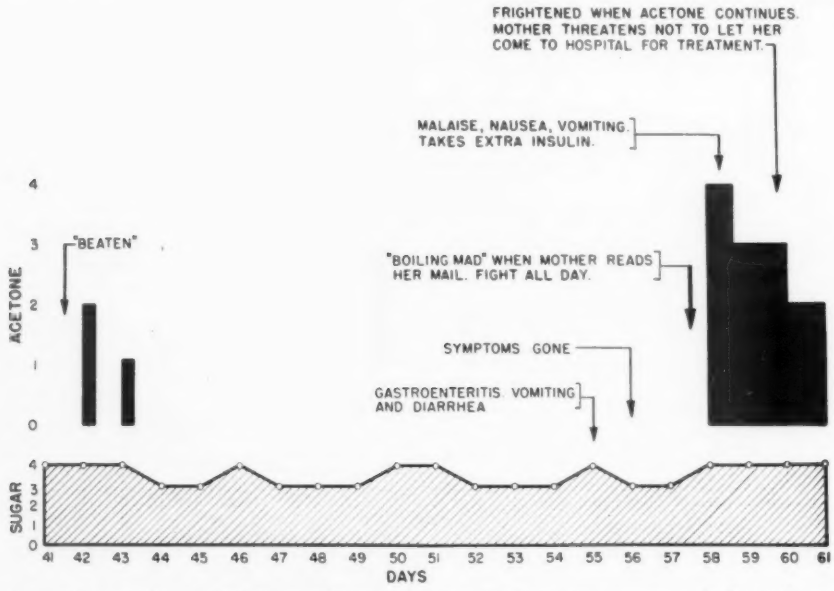
FRIGHTENED WHEN ACETONE CONTINUES. MOTHER THREATENS NOT TO LET HER COME TO HOSPITAL FOR TREATMENT.
MALAISE, NAUSEA, VOMITING. TAKES EXTRA INSULIN.
"BEATEN"
"BOILING MAD" WHEN MOTHER READS HER MAIL. FIGHT ALL DAY.
SYMPTOMS GONE
GASTROENTERITIS. VOMITING AND DIARRHEA
ACETONE
SUGAR
0 1 2 3 4
41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61
DAYS

FIG. 3.—Third 3 weeks of detailed correlation of urinary findings with events, attitudes and emotions.

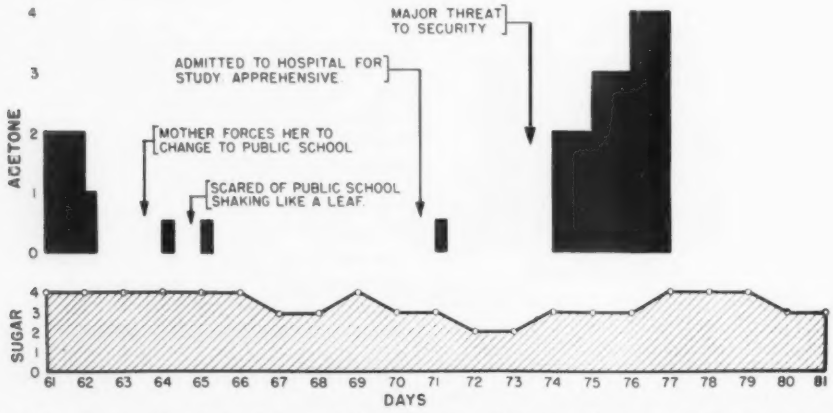
MAJOR THREAT TO SECURITY
ADMITTED TO HOSPITAL FOR STUDY. APPREHENSIVE
MOTHER FORCES HER TO CHANGE TO PUBLIC SCHOOL
SCARED OF PUBLIC SCHOOL SHAKING LIKE A LEAF.
ACETONE
SUGAR
0 1 2 3 4
61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81
DAYS

FIG. 4.—Fourth 3 weeks of detailed correlation of urinary findings with events, attitudes and emotions.

to her new dress while working at the hospital. She returned home in a frightened state and received a tongue lashing that lasted several hours. During the course of it her mother threw a frying pan at her. The emotional turmoil which accompanied this episode lasted for 48 hours. Acetone appeared in the patient's urine specimen on the morning after the turmoil began. She had developed polyuria during the night, was anorexic in the morning, and then vomited several times. On several occasions during the day she took orange juice and salty broth, as well as 2 extra doses of regular insulin. Despite this, acetonuria persisted for 48 hours.

During the next week, with her mother's consent, the girl was sent to a summer camp for diabetic children. During her stay there her diabetes remained in relatively good control. However, because she was lonely she

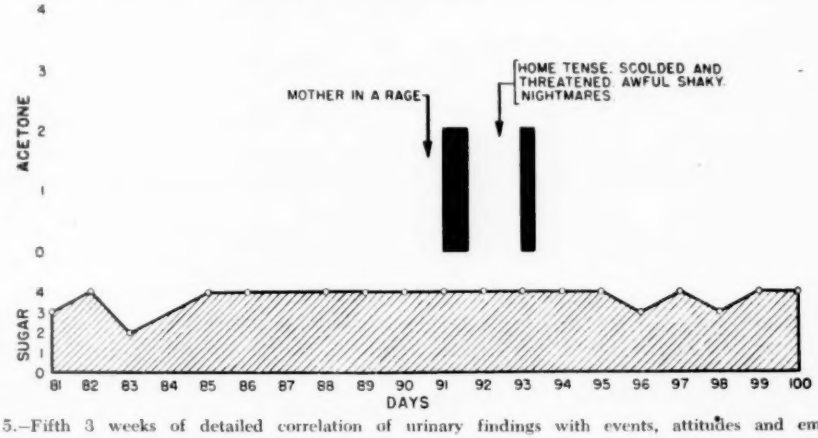
ACETONE
SUGAR
MOTHER IN A RAGE
HOME TENSE, SCOLDED AND THREATENED, AWFUL SHAKY, NIGHTMARES
DAYS
81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

FIG. 5.—Fifth 3 weeks of detailed correlation of urinary findings with events, attitudes and emotions.

came home unexpectedly on the 40th day of the observation period, upsetting her mother's plans for the ensuing week. The argument precipitated by her return home took place on the morning of the 42nd day. Acetone appeared in the noon specimen that day. It was present the following morning also.

For 2 weeks thereafter no ketonuria was reported. There were no emotional upsets during this time. On the 55th day the patient developed abdominal cramps, watery diarrhea, nausea, vomiting, and malaise, all of which lasted for about 12 hours. Her symptoms suggested that she had an infectious gastro-enteritis of moderate degree. She did not develop ketonuria.

Two days late however, after all her symptoms of gastro-enteritis had subsided, she became intensely angry upon discovering her mother reading her mail. Thereupon her mother upbraided her and called her an impertinent ingrate. The girl was "as mad as I have ever been in my life," but was too terrified to make further protest. The next morning her urine contained 4 plus acetone and she began to vomit. Seeing this, her mother made her more fearful by threatening "if you get sick again, I won't take you to the hospital." Acidosis continued for 5 days and the patient again treated herself with fluids and extra insulin.

She had hardly recovered from this episode when, on the 64th day, her mother forced her to stop going to a parochial school and made her enter a public high school. She was both resentful and fearful at this move. During the first 2 days at school she was "shaking like a leaf." There was a trace of acetone in her urine at noon each day.

On the 70th day of observation the patient was admitted to the hospital, to allow for a more detailed study of the relevance of her life situation to her bouts of acidosis. She was quite suspicious and somewhat fearful at the time of admission, and a trace of acetone was present in her urine. With reassurance she became more relaxed and soon adjusted to the ward routine. In order to regulate her activity it was arranged that she should have set chores to do under the supervision of the head nurse. She enjoyed this, feeling a sense of importance in her semi-official position. At the same time her constant association with the nurses made it possible to standardize effectively her diet. Her diet and insulin dosage were not altered. Examination at the time of admission showed no significant physical findings except obesity and a rather high tissue tur-

gor. The latter was thought to be associated with the high insulin dosage. After 3 days she was considered to be in a relatively calm, steady state. No acetone had been present in the urine since the admission specimen. Her fasting blood sugar was 200 mg. a/c at this time.

On the afternoon of the 74th day the girl's mother came to visit her physician. The two had a long and friendly chat, while the girl waited anxiously outside of the consultation room. When they left the room in serious and friendly conversation without more than a nod for her, she assumed that the worst had happened. She was allowed to gain the impression that both were angry with her. She confided later that she was convinced that her doctor (whom she regarded as her "only friend") had "gone over to Mother's side" and that the two were plotting against her. She felt angry, terrified, and helpless.

Shortly after this the nurses observed that she had a scowl on her face, and that she seemed preoccupied. She became restless, "jumpy," and complained of feeling "shaky." She had no appetite for her dinner, but forced it down. During the night she tossed restlessly in her bed and had several terrifying nightmares. About midnight she began to urinate frequently and in large quantities. The specimen contained 3-plus acetone.

When she was seen the next day she showed, in addition to restlessness and irritability, a startle reaction, acetone breath, dry tongue, rapid pulse, and cold moist palms. Her diet and activity were not altered. By evening acetone was 4+plus in all specimens, and attempts to reassure her were begun. While she was kept under observation, no other changes were made in her therapy. For 2 days fear, resentment, and ketonuria continued, subsiding slowly under reassurance.

Her subsequent course in the hospital was uneventful. By the time she left, her relation with her physician had been restored to its former state. At home she had 2 further bouts of ketonuria, each preceded and accompanied by threats to her security arising from strained relations with her mother similar to those described previously.

Discussion. Willms[11] has reported that a rise in blood ketone bodies occurs in response to exposure of relatively small areas of the body to Roentgen rays. Winkeler and Hebeler[12] have reported a similar rise in the blood ketone bodies after extreme physical exertion. Selye[10] has considered both of these phenomena as a part of the non-specific bodily reaction to stress which he calls the "alarm reaction." Inasmuch as threatening life situations which arouse emotional conflicts have been observed to initiate the alarm reaction, it may be that the ketonemia which appeared in this patient is another instance of this phenomenon.

The mechanisms by which the metabolic changes were produced is not clear. It appears that the fact that ketosis has been so readily elicited in this diabetic is in part related to her acute sensitivity to any threat which tends to disturb her relation to her mother. This relation to her mother is colored by intense and conflicting emotions at all times, even the "calmest." Her reaction to any disturbance of it includes not only ketosis, but also diuresis, restlessness, tachycardia, increased perspiration and a mood change characterized by anger, fear, and moderate depression. Part of this reaction – the tachycardia and increased perspiration, for example– apears to be mediated by the hypothalamic-sympathetic system. It seems reasonable to conjecture also that the pituitary, acting by itself and through the adrenal cortex, may play an even more important part in the reaction, especially in raising the blood sugar and increasing the severity of the diabetes. Perhaps the constant action of this later mechanism day after day may also explain why her diabetes is so severe and so resistant to treatment, and why her daily insulin requirement is so far above the 40 units required by the depancreatized human.

Conclusion. In an anxious, maladjusted, and severely diabetic 15 year old girl, it has been shown that stressful life situations which aroused the emotions of fear and rage were ac-

companied by alterations in the metabolism. One manifestation of these alterations was the appearance of ketonuria within approximately 12 hours of the onset of the stressful situation. With continuation of the stress under experimental conditions the ketosis was observed to continue to the point of clinical acidosis. Without change in diet or additional insulin the acidosis disappeared when the subject regained confidence and security.

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LONG TERM ANTICOAGULANT THERAPY FOR CARDIOVASCULAR DISEASES*

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Anticoagulant therapy has now been well established in the treatment of various thrombo-embolic conditions. Many authors,[2,3,4,6,8,9,12,13,14] including ourselves, have stressed the need for careful hospital and daily laboratory supervision. There are certain patients with recurring thrombotic and embolic tendencies who need anticoagulant therapy for long periods of time. In some instances, this may mean for the remainder of their lives. This is particularly true of patients with old rheumatic heart disease complicated by valvular damage and auricular fibrillation who release showers of emboli to the peripheral circulation from time to time. Recently, we reported in some detail such a group of patients who had been treated with anticoagulants.[14] Aside from the value of maintaining a state of cardiac compensation, this is the only therapy thus far suggested which reduces the incidence of embolic complications and thus favorably affects the clinical course of this type of patient.

There are other types of cases in whom it is advisable to continue anticoagulant treatment for an indefinite period. These include patients with phlebitis migrans, recurrent thrombophlebitis and certain patients with recurrent coronary thromboses and myocardial infarction in whom it is desirable to continue anticoagulant therapy as a prophylactic step against further recurrences. Nichol and Fassett[7] have reported experiences with this type of patient.

The purpose of this report is to present experiences with long continued anticoagulant treatment and examples of difficulties which may be encountered. To subject a patient to a daily intravenous puncture to procure blood for a prothrombin test is, in general, only feasible for a few weeks while he is in the hospital. After he leaves the hospital and becomes ambulant, a daily test is too time consuming, uncomfortable and expensive. It interferes greatly with the patient's daily life. The following plan has, therefore, been adopted for the care of such cases. Each patient's idiosyncrasies to dicumarol are studied while in the hospital. His daily requirements are evaluated. After 3 or more weeks of hospitalization, if the underlying disease is under control, the dicumarol requirements fairly stable, and the patient ambulant, he is discharged to his home on a specific daily dose of the drug. Thereafter, he reports twice weekly for prothrombin tests and a prescription of the daily dose. If the blood prothrombin level shows only minor fluctuations, this time interval is extended to once weekly. Some rare patients remain very stable and under these unusual circumstances the interval may be prolonged from 10 to 14

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days. In general, however, this is not to be recommended.

Serious study of this aspect of the treatment of ambulant patients with dicumarol has been carried out by the authors during the past 2 years. Since this treatment was known to be fraught with some risk, it was obviously important that patients be disciplined to take the exact amount of dicumarol prescribed and no more, and that they appear for tests as scheduled. For this reason, only intelligent and co-operative private patients have been selected for this regime.

The Link-Shapiro modification of the Quick method has been used to estimate the prothrombin time.[5,10,11] With the active rabbit lung thromboplastin used in our laboratory, the value for normal controls is 14 to 16 seconds. In treatment the aim is to determine a daily dose of dicumarol which will maintain the prothrombin time at from 30 to 35 seconds. This is termed the "therapeutic level."* Minor fluctuations outside of this range, but between 25 and 45 seconds, are not considered serious.

* To orient those readers who are accustomed to calculate prothrombin activity in percentage of normal, the comparative figures from our laboratory are listed below. Only active thromboplastin, which is tested daily against a normal person's blood and which gives a reading of from 35 to 41 seconds with a dilution, 1 part of plasma with 8 parts of saline, is used. If the thromboplastin does not come within this range, it is discarded and a new batch tested.

%		%		Sec.
100	plasma	0	saline	15±1
50	plasma	50	saline	17±1
25	plasma	75	saline	25±2
12.5	plasma	87.5	saline	38±3
8.33	plasma	91.67	saline	53±4

We have found that there is a great difference in the dose required to maintain this level from individual to individual. C. D. (Patient 13, Table 1) has an average weekly maintenance requirement of 175 mg. L. B. (Patient 1), on the other hand, requires a weekly dose of 800 mg. As will be noted in Table 1, there is no apparent correlation between body weight and the size of the dose in adults. Perhaps if all other factors which enter into this picture were equal, such a correlation would be more obvious. Age is not a factor, with rare exceptions. The average requirement in a stable patient remains fairly constant over a period of time. Patients standardized 1½ years ago usually require approximately the same amount of dicumarol today.

Some women show variations in the prothrombin time with their menses, but others apparently have no change. M. M. (Patient 8) usually requires an increase in dicumarol dosage just before and during her menses to maintain her therapeutic level. This has been observed for 16 months. During the menstrual week she needs 575 mg., during the other 3 weeks 475 mg. is usually sufficient. Studies of relationship of the estrogens to this finding are under way. In our experience, at therapeutic levels, dicumarol rarely increases menstrual flow in the absence of pathological states.

It appears probable that diet plays a rôle in the utilization of dicumarol.

Case 13. Mrs. C. D. could not be standardized on dicumarol dosage until she was placed on a high protein diet. After she was first stabilized in the hospital and then maintained on ambulant treatment, she occasionally developed sudden, high values of her prothrombin times. On one occasion, the prothrombin time was unexpectedly found to be 109 seconds. She was given intravenous vitamin K therapy. Upon close questioning, it was found that this patient's sudden prolongations of prothrombin time were subsequent to the ingestion of large amounts of whiskey. Reducing the consumption of whiskey resulted in a more uniform test from week to week.

Two possible explanations occur: (a) that the alcoholic consumption in some way temporarily interfered with

prothrombin production in the liver, (b) that the intake of protein was significantly reduced when considerable alcohol was taken. The relation of protein intake to dicumarol utilization was called to our attention personally by Jorpes[6] and by Zilliacus[16] during their recent visits to this country.

In most patients there has been little difficulty in administering the treatment and very encouraging and successful results have been obtained. An example of such a case follows:

Case 2. J. C., a 53 year old housewife, who developed rheumatic fever at 28 years of age, and had 5 recurrences thereafter. She developed auricular fibrillation approximately 5 years before the present hospital admission. It has been paroxysmal, with great variations in the duration of attacks. Her first recognized embolus occurred in 1944. This was cerebral and she became unconscious. She remained in bed for approximately 6 weeks and she made a complete recovery. The second embolus occurred on May 30, 1946, producing a sudden complete loss of consciousness. This probably was cerebral also. In June 1946, she had emboli to both legs. On July 7, 1946, she developed a sharp pain in the right hip and also one in the chest followed by bloody sputum which was probably secondary to a pulmonary infarction. On July 14, 1946, she had an embolus to the right leg. Anticoagulant therapy was not started at that time, but was begun on September 24, 1946. She received dicumarol while in the hospital for 1 month, since which time she has been ambulatory. She requires approximately 500 mg. of dicumarol per week. On December 16th, she began to have excessive menstrual flow which continued for approximately 10 days. Her prothrombin time ranged between 24 and 28 seconds; therefore it seems unlikely that this was responsible for her excessive flow. The dicumarol was discontinued and vitamin K, 2 doses of 64 mg. each, was given. A gynecologist believed that the excessive flow was due to menopausal changes and a dilatation and curettage was performed, followed by irradiation. She then resumed dicumarol. There have been no emboli since she first began dicumarol.

Case 3. E. S., a 42 year old housewife, had typhoid fever at 3 years of age, scarlet fever at 4 years, and rheumatic fever at 5 years. Rheumatic heart disease was recognized during the 6th year. Chorea was diagnosed at 6, 10 and 12 years of age. Since the age of 33 her heart has been in a state of auricular fibrillation, and during these years she has taken digitalis daily. In 1935 she had an embolus to the left groin and also a pulmonary embolus. In 1942 she had a left cerebral embolus which produced a right hemiplegia from which she made a complete recovery. During the years of 1943 to 1944, it was estimated that she had at least 6 emboli, which were apparently small, in various locations throughout her body. In December, 1945, she developed 2 emboli, one renal and one mesenteric. In January, 1946, she developed her 13th definite embolus which was pulmonary, and in September, 1946, her 14th embolus which was also pulmonary. On November 15, 1946, she became decompensated. Two days later there occurred the 15th embolus to the right arm. This produced coldness, blanching, loss of pulsation below the elbow, and appeared to endanger the arm. On November 19th, she developed the 16th embolus which was to the left leg; on November 25th, a 17th embolus to the right lung field; and on December 3rd, her 18th to the right lower quadrant of the abdomen which produced shock, paralytic ileus and later blood in the stool. On December 3rd, she developed her 19th embolus which was to the left leg. On December 20th, she developed an embolus which was to the left forearm and produced marked generalized shock. The patient was acutely ill. Her outlook appeared extremely serious.

On the day of her 20th embolus, because of her desperate condition, she was started on anticoagulant therapy despite the blood in her stools, which was believed to be secondary to a mesenteric infarction. She received 52.5 mg. of heparin intravenously at 9:00 p. m., December 6th; 52.5 mg. at 1:00 a. m., and 50 mg. at 6:15 p. m., December 7th. She was also given 300 mg. of dicumarol on December 6th, followed by daily doses of 200 mg., and thereafter was regulated in accordance with the indications of her prothrombin times. She was continued for 1 month on this regimen while in the hospital. Her average requirement of dicumarol was 300 mg. weekly. Following the initial administration of anticoagulants, there was an immediate cessation of her embolic phenomena and a completely uneventful course. She was discharged from the hospital on January 6, 1947. She has since continued to receive anticoagulant therapy while ambulatory. She has had several episodes of ecchymoses of a very mild degree. Her prothrombin time has in general been kept between 25 and 35 seconds, the highest having been 44 sec-

onds. No further embolic episodes have occurred in a period of 15 months. The patient's general condition is excellent; she is able to travel and does so freely and without difficulty whenever satisfactory prothrombin studies can be arranged. By planning, it was possible for her to travel from New York to the Pacific Coast and return, having had prothrombin tests weekly at reliable laboratories en route. The trip was without untoward incident. Her heart continues in a state of compensated auricular fibrillation.

CASE 1. L. B., a 39 year old housewife, developed rheumatic fever at 4 years of age. From then until she was 12, she had multiple attacks of rheumatic fever with the development of a heart lesion. In 1941 she developed auricular fibrillation and was found to have mitral stenosis with cardiac decompensation. In February, 1946, she had a severe saddle embolus. She was then given heparin for 2 weeks. The embolus apparently divided, descending into both legs and leaving her with occlusion of the major arteries below the knees bilaterally. In 1946, between February and June, she suffered 6 embolic episodes, involving her legs and also her abdomen and brain. In September, 1946, she had an embolus to her right foot, and again one to each leg. On November 2, 1946, she developed a cerebral embolus which produced dizziness, diplopia, slurring of speech, involuntary twitching of the right arm, occipital headaches and loss of convergence of the left eye. She was admitted to The New York Hospital on November 3rd and dicumarol was started at that time. She remained in the hospital for 1 month, since which time she has been ambulatory. Her average weekly requirement of dicumarol is somewhat higher than that of most patients. She needs approximately 800 mg. per week to maintain a level between 28 and 35 seconds. She has had no further emboli and leads a rather active life.

CASE 7. Colonel R., age 57, developed phlebitis of the right leg in July, 1944, while in military service. Pulmonary emboli occurred in August. In November, 1944, the phlebitis recurred in the right leg. A femoral vein ligation was performed. In January, 1945, pulmonary emboli again developed. His inferior vena cava was ligated. In February both legs were swollen. Phlebitis was found in the left leg in March. By June, phlebitis had involved the veins of his anterior abdominal wall. He was retired from military service because of disability. He continued to have bouts of phlebitis in both his legs and arms. We saw him for the first time in May, 1946. He was hospitalized for 2 months and placed on anticoagulant therapy. He remained free of phlebitis for 4 months, and then allowed his treatment to lapse. Phlebitis recurred in his arm. Dicumarol was resumed on what will probably be a permanent basis. He is now free of any active phlebitis. He has resumed moderate activity after nearly 3 years of invalidism.

The hazards of ambulatory treatment are well illustrated by the following case:

CASE 5. H. S., age 29, who suffers from a migratory thrombophlebitis. When maintained on proper dicumarol dosage, his phlebitis is quiescent. When his prothrombin time falls below 25 seconds, he almost invariably develops thromboses in the veins of his legs or arms. A dose which is too great for his immediate needs sends his prothrombin time soaring. He then tends to hemorrhage, usually under the skin. He has, therefore, a very narrow therapeutic zone within which to prevent thrombosis on the one hand and hemorrhage on the other. He is exceptional in this regard. In July, 1947, the chemist, who was working on this case with us and is expert at determining prothrombin times, was suddenly stricken with a coronary thrombosis himself. (He was treated with anticoagulants and constitutes Case 16 in this series). His technical assistant then substituted for him. As frequently happens with technicians who are inexperienced with this test, certain errors occurred during the first few days in the case of H. S. (Case 5). On one day when the prothrombin was reported as 24 seconds, he suddenly developed large subcutaneous ecchymoses. He was admitted immediately to the hospital where his prothrombin time was found to be 180 seconds by our research laboratory. He was given 72 mg. of synthetic vitamin K every 4 hours for 4 doses, and one 500 cc. transfusion of fresh blood. His prothrombin time fell gradually to therapeutic levels and there was no further bleeding. Seven months later he again encountered difficulty. At this time he was fairly well standardized on a daily dose of 50 mg. of dicumarol. One day his prothrombin time was found to be 33 seconds; seven days later it was 108 seconds. He was given 3 doses of synthetic vitamin K, 72 mg. each, 4 hours apart. The next day the prothrombin time had fallen to 83 seconds, the following day to 57, and 2 days later it was 21 seconds. At this level, thrombi promptly developed in the superficial veins of the right calf. In spite of these occasional difficulties, he has continued to work at a responsible job during the past year.

One cannot belittle the hazards of dicumarol therapy with this man, yet they must be weighed against the risks of his serious disease—thrombophlebitis migrans. Prothrombin times should be performed twice weekly for the proper control of this patient.

Another case illustrated further the danger of unreliable laboratory data.

Case 6. G. G. a woman, age 25, was seen in consultation in a suburban hospital. She had recurrent thrombophlebitis involving deep pelvic and abdominal veins, and probably one renal vein. While awaiting transfer to The New York Hospital, she was given dicumarol. After 5 days, her prothrombin time was reported by the laboratory of the suburban hospital as 27 seconds. The following day, she was admitted to the New York Hospital. The prothrombin test was carried out by our research laboratory. No end point could be found. It was reported as 300 seconds plus, the longest time we record. (It is quite unlikely that this rise occurred in 24 hours). This patient was given intravenous vitamin K and 2 transfusions of fresh blood during the next 3 days. The prothrombin time gradually fell to a therapeutic range. She experienced no bleeding except for a slight oozing from the gums when she sucked on them. She was discharged later from the hospital and has remained on ambulant treatment without difficulty for the past 6 months.

M.M., age 44, Case 8, previously referred to, has also on 2 occasions inexplicably developed high prothrombin levels that required intravenous vitamin K injections.

It is now routine to give 2 doses of 72 mg. each of vitamin K intravenously at 4 hour intervals when the prothrombin time reaches 60 seconds or more. This has almost without exception been sufficient in cases with prothrombin times of less than 100 seconds.

An example of another type of difficulty is cited as follows:

Case 4. M. S., a school teacher, 51 years of age, had rheumatic fever at the age of 23 with subsequent mitral stenosis. Beginning in 1942, she developed auricular fibrillation. In the summer of 1945, she developed a pulmonary embolus. This was followed during the next year by emboli to the right leg, the abdomen, the left leg, and then again to the abdomen. Anticoagulant therapy was begun. She had no further emboli. She had a very difficult domestic situation to cope with and began to show emotional instability. It became doubtful that she would continue to follow explicit directions, so her anticoagulant treatment was discontinued. Seven days later, she had an embolus to the right area, blocking the brachial artery at its bifurcation.

It is likely that many of these patients should justifiably continue anticoagulant treatment for years to come, perhaps for life, or until better therapeutic means are developed. They must for the present, at least, take their required doses of dicumarol and have periodic prothrombin tests, just as a diabetic must take his insulin daily and have his urine and blood sugar determinations performed periodically.

Toxicity. The problem of overdosage has already been mentioned. The possibility of serious damage to the liver, kidney or other organs during prolonged administration of dicumarol has been carefully considered. We have found no clinical evidence of such toxicity in this group of patients. This confirms the first report of one of us[15] on the use of dicumarol. It agrees with the report of Nichol and Fassett[7] of an autopsied patient who had received dicumarol for 21 months.

Summary and Conclusions. (1) A group of 19 patients has been maintained for from 5 to 20 months (average 11 months) on dicumarol. Their prothrombin time has been checked every 7 to 14 days after having been carefully standardized at more frequent intervals during several weeks or months of hospitalization.

(2) This method requires constant vigilance on the part of the physician, and faithful cooperation from the patient. It necessitates a laboratory skilled in performing prothrombin times.

(3) No effort has been made to evaluate statistically the results of this therapy in this report. The object has been

to make available experiences with this clinical problem and to discuss the manner in which they have been met.

(4) Neither age nor weight constitutes the determining factor in the dosage requirements for this form of treatment.

(5) Diet apparently plays some part in the dicumarol requirements. An adequate protein intake helps to stabilize the requirements in some patients. Excessive alcoholic intake may affect the requirements.

(8) No discernible damage to the liver or kidneys has occurred in any patient as a result of the prolonged administration of dicumarol.

(9) No thrombo-embolic episode has occurred in these patients while their prothrombin time has been at a "therapeutic level" (prothrombin times above 30 seconds).

(10) There have been no deaths in this series despite the seriousness of the condition of many of these patients at the time of onset of the therapy.

TABLE 1.—PATIENTS RECEIVING DICUMAROL THERAPY

No.	Name	Diagnosis	Months on Dicumarol (to May 1, 1948)	Average Weekly Dose (Mg.)	Age (yrs.)	Weight (lbs.)
1.	Mrs. L. B.	Rheumatic Heart Disease Mitral Stenosis Auricular Fibrillation Multiple Emboli	18	800	39	110
2.	Mrs. J. C.	" "	20	500	53	125
3.	Mrs. E. S.	" "	17	300	42	112
4.	Mrs. M. S.	" "	9	700	51	137
5.	Mr. H. S.	Phlebitis Migrans	11	300	29	167
6.	Mrs. G. G.	" "	9	350	25	126
7.	Col. G. R.	" "	12	300	57	166
8.	Mrs. M. M.	Recurrent Phlebitis	19	500	44	135
9.	Mr. K. N.	" "	16	500	56	205
10.	Mr. A. S.	" "	9	450	44	155
11.	Mrs. J. S.	" "	12	400	31	140
12.	Mrs. E. W.	" "	12	700	48	203
13.	Mrs. C. D.	" "	12	175	40	145½
14.	Mr. H. C.	" "	8	550	52	158
15.	Mr. A. H.	Coronary Artery Thrombosis with Myocardial Infarction	9	350	47	165½
16.	Dr. M.	" " "	9	315	50	144
17.	Mrs. A. M.	" " "	5	300	49	116
18.	Mr. S. D.	" " "	5	350	52	183
19.	Mrs. C. S.	" " "	8	400	66	158

(6) Prothrombin times of more than 300 seconds have occurred without serious hemorrhage. Sixty seconds is regarded as the upper limit of the desirable and safe therapeutic range.

(7) Excessive prothrombin times have all been controlled with vitamin K in adequate doses and whole fresh blood transfusions.

(11) No serious hemorrhages have developed in any of these patients despite their having been almost constantly under dicumarol therapy.

(12) This method of therapy has enabled most of these patients to lead fairly normal social lives, and, where necessary, to support themselves and their families. They have been able to

accomplish much that had been beyond their possibilities prior to the use of dicumarol because of frequent emboli and thrombotic episodes. This statement includes those patients who have occasionally developed complications such as have been described.

(13) The further development of the ambulatory treatment of thrombo-embolic diseases with anticoagulants will greatly broaden its application and usefulness.

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EFFECTS OF MYANESIN UPON THE CENTRAL NERVOUS SYSTEM*

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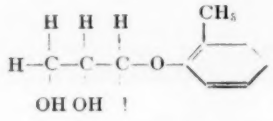
Myanesin, one of a series of alpha substituted glycerol ethers was investigated by Berger and Bradley[1,2,3] who found that it produced in animals a profound muscular relaxation without unconsciousness. In higher doses they noted analgesia, ataxia, arousable sleep and complete paralysis. It is a local anesthetic. They thought that the chief action of the drug was upon reflex excitability of the spinal cord, because the convulsions of strychnine were effectively prevented while those from metrazol (leptazol), supposedly acting upon higher centers, were much less influenced. With large doses a peripheral curare-like effect was demonstrated in nerve-muscle preparations. Mallinson[9] first employed myanesin in humans to aid relaxation in general anesthesia.



Formula of Myanesin (British Drug Houses), Tolserol (Squibb); 3-ortho-toloxy-1, 2-propanediol.

The chief clinical interest in the compound stems from the observation by Stephen and Chandy[11] that the drug abolished the tremors and rigidity of Parkinsonism and reduced the movements of choreo-athetosis at a dose which did not impair strength or consciousness. In this action the drug is unique. Electroencephalogram patterns of their cases were unaltered by the drug. From their observations they concluded that the chief site of action was upon structures lying between the cortex and the spinal cord. Schlesinger *et al.*[10] found, in addition, with somewhat larger doses, a depressant effect on spinal cord reflexes.

We have been investigating the effect of myanesin upon various pathological states in order to determine its sites and modes of action and to evaluate its therapeutic possibilities. We have been able to confirm several of Stephen and Chandy's observations and to add some others of interest. The usual common effects of the dose we employed consisted of a subjective sense of warmth, relaxation and slight giddiness, but not impairment of mental faculties. Two patients became faint when placed upright while under drug action. Nystagmus, slurred speech and loss of eye convergence were ordinarily observed. Normal electroencephalographic patterns were unaltered.

The tremor of Parkinsonism was abolished (in 7 cases) and choreoathetotic movements were suppressed greatly or completely (in 4 cases)

* This study was supported in part by the Kirby-McCarthy Fund.

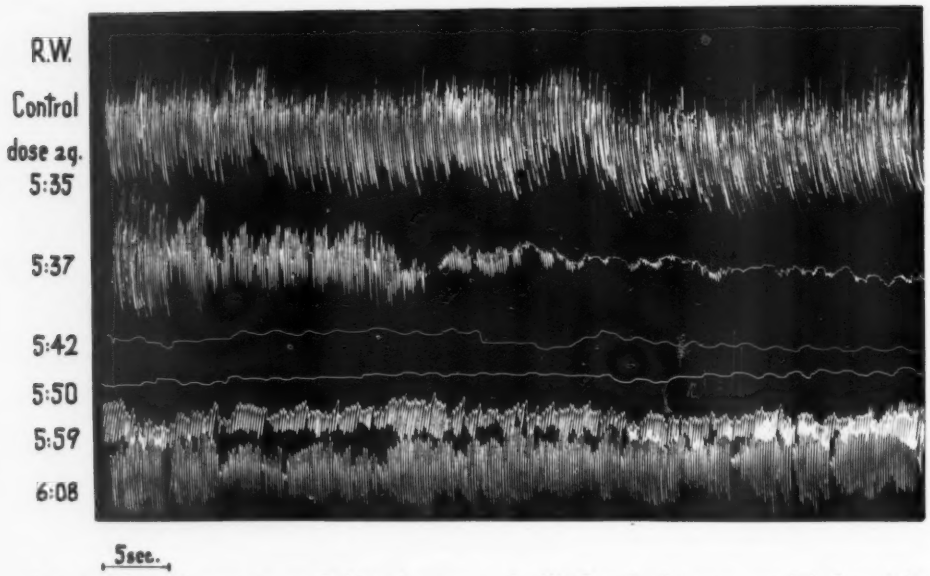


FIG. 1.—Effect of myanesin on Parkinsonian tremor. R. W. Record of tremor recorded from index finger connected by cord to muscle lever writing on smoked drum. Record continuous in each line, beginning at stated time. First line control. Second line, 2 minutes after start of infusion, shows great decrease in amplitude and frequency of tremor, which is completely (lines 3 and 4) suppressed for about 20 minutes, then gradually returns. Movement in lines 3 and 4 are due to respiration. Time 5 sec. Total dose 2 gm. myanesin.

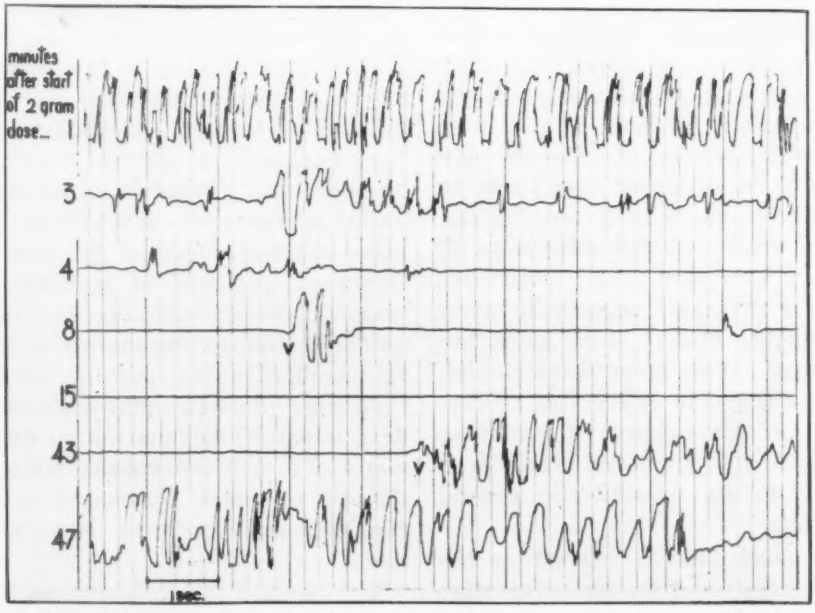


FIG. 2.—The effect of myanesin upon involuntary choreo-athetotic movement in a case of Wilson's disease (Hepato-lenticular degeneration). A fixed photo-electric cell is activated by a light attached to subject's finger and the potential lead into a standard electroencephalograph amplifier. Record continuous in each line beginning at stated minutes after start of intravenous infusion of myanesin. In lines 4 and 6 the V indicates voluntary movement intended to provoke the choreoathetosis. Movements suppressed about 40 minutes. Infusion lasted 12 minutes. Time 1 sec.

(Figs. 1 and 2). Rigidity was greatly decreased or abolished in these cases, but strength was unaltered and tendon reflexes were little affected. Senile tremor was greatly improved. On the other hand, the intention tremor of multiple sclerosis was increased (in 2 cases). Two cases of chorea (1 Huntington's and 1 congenital) were unaltered. Brief discharges associated with anterior horn cell disease were unaffected; we observed no alteration of organic facial hemispasm or of fasciculations in amyotrophic lateral sclerosis. In 1 case of tetanus the spasms were abolished.

TABLE 1.—EFFECT OF MYANESIN ON HANDGRIPS
DYNAMOMETER READINGS AFTER MYANESIN
Number of Trials in Parenthesis

Case	Before Drug		After Drug	
	Average Reading	Range	Average Difference from Control	
			10 Min.	20 Min.
1. Facial Tic	53	+5 to −3	−3	0
	(2)		(1)	(1)
2. Multiple Sclerosis	53	+7 to −8	+2	0
	(2)		(1)	(1)
3. Multiple Sclerosis	20	0	0	−5
	(2)		(2)	(2)
4. Parkinsonism	26	+5 to −6	+2	−1
	(10)		(3)	(3)
5. Choreo-Athetosis	42	+3 to −2	+1	+1
	(5)		(2)	(3)
6. Wilson's Disease	61	+19 to −16	+6	0
	(7)		(3)	(4)
7. Tabes	94	+36 to −14	−19	−18
	(7)		(8)	(5)

Strength was unaltered in 16 cases without pre-existing weakness (Table 1), but 2 cases of multiple sclerosis developed a profound increase in weakness in the lower extremities although the upper extremities were unaffected. At the same time there was a decrease in tone. One tabetic had an increase in his ataxia and perhaps some decrease in strength. It is apparent that weakness is more easily developed in the presence of pre-existing disease of the pyramidal, and possibly other, systems.

Spontaneous pain was abolished and the exaggerated second-pain in response to pinprick of a tabetic was reduced, without loss of pinprick perception. Causalgic pain was relieved (1 case) for a short time and improved for 24 hours. Phantom limb pain, in contrast, was unaffected (1 case). Stephen and Chandy, and Schlesinger *et al.* had noted an effect upon pain.

These clinical observations suggest that myanesin in the doses used, has a differential action upon the basal ganglia, brain stem and perhaps thalamus.

To test further the possibility that pathological discharges from thalamus or related structures might be influenced by this agent, we have studied the electroencephalograms of petit mal cases, in which large areas of brain cortex are "fired" simultaneously, possibly from thalamic or subthalamic nuclei[6,7,8]. In 6 cases of true petit mal without general seizures these discharges were abolished by this agent (Figs. 3 and 4). By contrast, convulsive cases with focal cortical abnormalities and 2 cases of petit mal associated with generalized seizures, the so-called "petit mal variant" of Lennox, and supposedly the result of cortical

damage, were unaffected. These observations, taken with the fact that normal electroencephalographic patterns were unaltered by this dose, suggest that myanesin acts in these cases by preventing the discharges arising in subcortical nuclei.

Since improvement in certain psychoses has been obtained by severing the connections of the thalamic nuclei and various parts of the cortex[4] or by a destruction of thalamic nuclei,[13] a trial of this agent which appears to affect the thalamus would seem to be profitable. Preliminary observations on 3 cases have proved of interest. A patient with reactive depression was improved for the period in which the drug was active; a deteriorated negativistic schizophrenic became communicative for the first time in years; and an agitated patient who would not respond became calm and communicative under the action of the drug. These experiences are being extended.

Although said to be effectual orally and intramuscularly in animals, we have used the intravenous route. Injection of a 1 or 2% solution rapidly up to 1 gm. establishes the action. From this dose the effect lasts a matter of a few minutes to 1 hour. To maintain action after the initial dose it is necessary to infuse at about 1 mg. per kilogram body weight per minute. This is about the amount required to maintain a constant blood level in animals.[12] It seems likely that effective action requires the maintenance of a critical blood level of an agent which is rapidly inactivated. The maximum total dose we have used is 87 mg. per kilogram body weight.

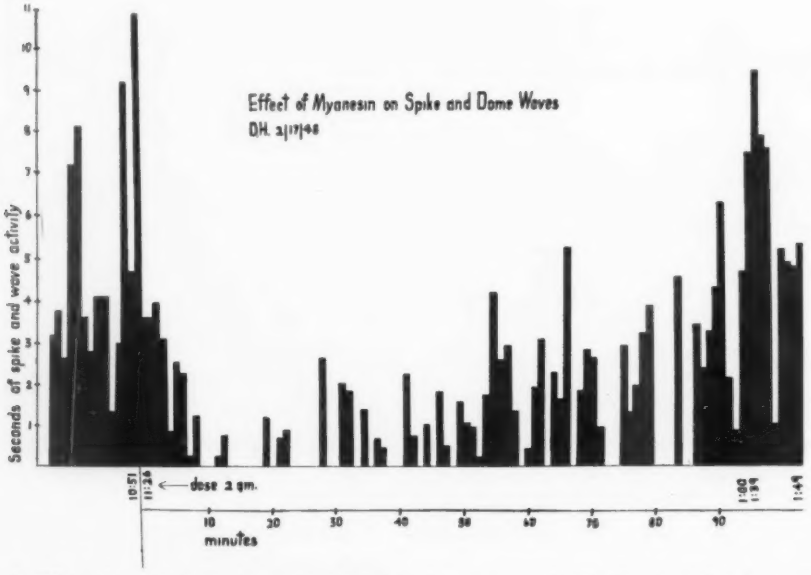


FIG. 3.—Effect of myanesin on electroencephalograph of true petit mal. The line in each minute occupied by spike and dome formations is indicated on ordinate. Record continuous. Dose 2 gm. at 11:26. Minutes after infusion indicated on abscissa. A sharp drop in activity lasts about 60 minutes.

We have observed no untoward reactions. Although the drug is hemolytic we have found no hemoglobinuria. Jacobs *et al.*[5] find that it acts as a detergent on red cells. We have observed no local venous thrombosis.

The action of myanesin appears to

be differentially selective for the cluster of subcortical nuclei which make up the basal ganglia, thalamus and brain stem. With increasing dosage the conducting mechanisms of the spinal cord, both motor and sensory, are blocked, and cortical activity is depressed. Finally, a peripheral neuromuscular block ensues. But apart from this selective affinity of action, the evidence from pathological cases suggests that the drug cuts down any repetitious, prolonged or grouped discharge.

relief of pain. Examples are: as an adjunct to anesthesia and, as Schlesinger *et al.* suggest, for painful lumbar spasm and manipulation of joints. In the case of Parkinsonism rigidity and tremor and athetosis the drug unquestionably has a greater effect than any other therapy short of narcosis. This fact alone should encourage a search for similar, but longer-acting compounds. The rapid inactivation of the drug still limits its usefulness in chronic conditions.

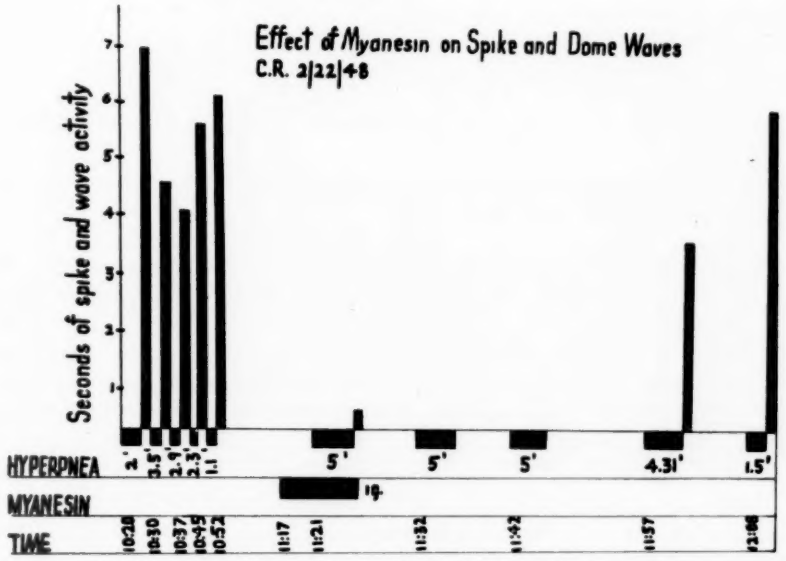


FIG. 4.—Preparation of graph similar to Fig. 3. Bursts of spike and dome waves were provoked by hyperpnea. In each control trial they appeared within 3.5 min. Five minute hyperventilations 4, 15 and 25 min. after start of infusion did not produce bursts until 40 minutes after infusion when they reappeared.

Tremor, athetosis, rigidity, spasticity, the spasm of tetanus, and prolonged pain, all may be abolished by myanesin at a time when brief twitches, such as choreic jerks and fasciculations and the perception of pinprick are unimpaired. This, in turn, may depend, as with barbiturates, upon a depression of synaptic transmission.

As matters now stand, myanesin may be used, wherever intravenous infusion is feasible, to achieve a transitory relief of tremor, relaxation of tone, and

Summary. Myanesin, an alpha substituted glycerol, which was found by Stephen and Chandy to have a depressant action on the parts of the nervous system lying between the cortex and the spinal cord, was administered to a variety of pathological cases in order to analyze its action and to test its therapeutic possibilities. With intravenous dosage the effect is quite transitory, lasting from a few minutes to a few hours.

Parkinsonian tremor is abolished

without impairment of strength or consciousness, an action which is unique. Choreo-athetosis is reduced or abolished, confirming other observations. Senile tremor is improved but the tremor of multiple sclerosis was increased. Chorea (Huntington's and congenital) was unaffected. Brief discharges associated with anterior horn cell disease were not affected as in fasciculations of amyotrophic lateral sclerosis and organic facial hemispasms. On the other hand, the spasm of tetanus was abolished.

The tone of Parkinsonian cases was reduced. Strength was unaltered with the dose used except in the presence of pre-existing lateral column disease.

A sensory effect was noted in the abolition of tabetic pain and an exaggerated second pain response, and in causalgic pain. Phantom limb pain was unaltered.

These observations suggested a differential depression of function in the basal ganglia, brain stem and thalamus. This conclusion was strengthened by the abolition of petit mal discharges by a dose which did not affect the normal electroencephalogram or the discharge from a cortical scar.

In view of the results of thalamotomy and prefrontal lobotomy, the agent was tested on certain psychotic cases with promising results. This aspect of its action is being studied further.

The transitory action of the drug limits its therapeutic possibilities.

We wish to express our appreciation to Dr. Donald S. Searle of Burroughs Wellcome Company and Dr. H. Sidney Newcomer of E. R. Squibb & Sons Co., for part of the drug used – also to Dr. Sidney J. Deichelmann and Dr. Harvey Bartle for their cooperation.

Addenda. The characteristic myanesin action can be obtained from oral medication. Repeated trials on 8 cases of Parkinsonism resulted in moderate relief of tremor for 30 to 60 minutes following 2 to 3 gm. doses. Occasionally the larger dose was ineffectual, and inconstant responses frequently occurred from similar doses.

No decrease in effect occurred in 2 subjects taking 3 gm. twice daily for 1 month; and in another a constant effect on tremor was attained throughout 4 hours of continuous intravenous infusion. A continued reduction of spasticity could be obtained by an hourly dosage of 2 gm. throughout a 2 week period, in a patient with post-encephalitic tetraplegia.

A drop in the leukocyte count to 3000 occurred in 2 subjects following large doses of myanesin. This effect is being investigated further.

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THE TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH MASSIVE DOSES OF SYSTEMIC PENICILLIN

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Penicillin gives better results in pneumococcic meningitis than any other therapeutic agent yet discovered. Among the 40 patients treated in our clinic with sulfonamides alone, 93% died[34] while only 62% died among the 66 patients who received a combination of sulfonamides and penicillin. Other investigators have obtained case fatality rates with the use of penicillin ranging from 8% to 64%. By tabulating the series of cases containing 5 or more patients, we were able to find 319 cases of pneumococcic meningitis in the literature in which penicillin was the mainstay of treatment.[2,3,9,10,12,14,15,29,33,36,37,38] Most of these patients received sulfonamides in addition and almost all of them received penicillin by both the intrathecal and intramuscular or intravenous routes. Death occurred in 157 cases, giving an average case fatality rate of 49.2%. This compares favorably with an average case fatality rate of 94% found among all the patients treated with sulfonamides in the District of Columbia for 4 years.[5]

The orthodox regimen for the treatment of pneumococcic meningitis at the present time consists of daily intrathecal injections of 10,000 to 20,000 units of penicillin in conjunction with 200,000 to 1,000,000 units daily in divided doses systemically. Sulfadiazine or sulfamerazine is usually given in addition. When evidences of subarachnoid block appear, intraventricular or intracisternal injections of penicillin are recommended. In addition to the fact that only 51 recover among every 100 patients subjected to this type of treatment, the regimen itself has several disadvantages:

(1) Local instillation of penicillin may cause an irritative arachnoiditis, manifested by pleocytosis[26] and sometimes by subarachnoid block. The latter may require intraventricular and cisternal injection of penicillin with their attendant dangers or may result in hydrocephalus.

(2) Myelitis and radiculitis following intrathecal administration have been reported by several observers.[7,32,34,35] Clinical and experimental studies have demonstrated that when penicillin is

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applied to the cerebrum, areas of necrosis may be produced[30] and convulsions may occur.[22,24,35]

The distribution of penicillin throughout the cerebrospinal fluid is not always assured when it is injected intrathecally. McCune and Evans[20] reported in one instance that only a trace of penicillin had reached the right ventricle 2 hours after 7500 units had been introduced into the lumbar subarachnoid space. This is in contrast with the fact that when penicillin is administered systemically the concentration in the lateral ventricle is higher than that found in the lumbar intrathecal space, as shown by two of us with Dumoff-Stanley.[6]

Certain other disadvantages accompany the direct injection of penicillin into the cerebrospinal fluid. One of these is the danger of infection following lumbar puncture.[11] Another is the amount of work required on the part of physicians and attendants in doing repeated lumbar punctures, and the discomfort and annoyance to the patient resulting from these procedures.

Intrathecal penicillin is almost universally advocated for the treatment of pneumococcic meningitis because many investigators[1,8,13,16,23,27] have found that when penicillin is administered systemically, none diffuses into the cerebrospinal fluid. On the other hand, there are some reports[4,6,17,19,21,28]

TABLE 1. PATIENTS WITH PNEUMOCOCCIC MENINGITIS TREATED WITH ONE MILLION UNITS OF PENICILLIN EVERY 2 HOURS

						TREATMENT				
Patient	Age (yrs.)	Type of Pneumococcus	Associated Infections	Day of Illness Treatment Begun	Duration of Penicillin Treatment (days)	Sulfonamides	Intrathecal Penicillin	Result	Day Temperature Dropped Below 101°F.	Day WBC Below 30
Baby Sh.	3 days	8	No focus found	?	<1 day	0	0	D	—	—
J. F.	8 mos.	14	?	?	<1 day	1 dose	0	D (24 hrs.)	—	—
J. G.	10 mos.	12	pneumonia	2	7 hrs.	Yes	0	D (7 hrs.)	—	—
M. H.	2 yrs.	7	head injury	2	6 days	Yes	0	R	5	6
P. A. W.	2 yrs.	14	pneumonia	1	7 days	0	0	R	3	7
G. T.	33 yrs.	13	?	?	10 days	Yes	1	R	2	19
P. M.	38 yrs.	19	pneumonia empyema endocarditis	?	9 days	Yes	0	D	—	—
H. L.	40 yrs.	22	?	?	12 days	Yes	0	R	2	5
L. S.	40 yrs.	4	?	18	13 days	Yes	Yes	R	3	32
A. R.	41 yrs.	8	pneumonia	4	7 days	0	0	R	4	19
L. H.	43 yrs.	3	otitis	4	13 days	Yes	0	R	4	4
T. O.	47 yrs.	12	?	?	16 days	0	0	R	4	8
V. A.	49 yrs.	12	arthritis	3	21 days	Yes	0	D	—	—
D. G.	52 yrs.	7	?	2	<1 day	Yes	0	D (11 hrs.)	—	—
A. C.	56 yrs.	not typed	otitis	?	9 days	0	0	R	2	4
N. V.	56 yrs.	8	endocarditis	11	<1 day	Yes	Yes	D (13 hrs.)	—	—
W. H.	56 yrs.	12	pneumonia arthritis	5	17 days	Yes	0	R	7	15
F. A.	57 yrs.	20	pneumonia	5	<1 day	Yes	Yes	D (6 hrs.)	—	—
M. B.	68 yrs.	23	?	?	7 days	0	0	R	3	10
G. L.	80 yrs.	9	?	4	7 days	0	0	R	2	8
W. R.	81 yrs.	18	No focus found	?	17 days	0	0	R	21	28

which indicate that low concentrations of the antibiotic are found in the cerebrospinal fluid, especially when fairly large doses are given systemically, particularly when meningitis is present. When Schwemlein and his co-workers[31] reported that detectable concentrations of penicillin were present in 100% of patients who received 20,000,000 units or more of penicillin during the course of 24 hours by continuous intravenous injection, we decided to treat patients with 1,000,000 units of penicillin intramuscularly at 2-hour intervals.

The concentration of penicillin in the blood and cerebrospinal fluid was determined in the case of 21 patients, with and without meningitis, at various intervals after beginning the administration of the antibiotic. Small amounts of penicillin were present in all patients within 60 minutes after intramuscular injections were begun. After 8 hours the spinal fluid concentrations were between .08 and 1.25 units per cc. The concentration of penicillin in the blood immediately prior to an injection (*i.e.*, 2 hours after the previous injection) varied between 2.5 and 20 units per cc.

We have treated 21 patients with pneumococcic meningitis, using doses of 1,000,000 units of penicillin every 2 hours (Table 1). Two of these patients were given a single intrathecal dose of 20,000 units of penicillin and 1 an intrathecal dose of 25,000 units. Thirteen patients were given sulfonamides in addition to penicillin. Eight patients died, 6 of them within 24 hours of the start of therapy. Penicillin therapy was continued for approximately 1 week after the temperature made its principal fall and the signs of toxicity began to recede, provided that the cerebrospinal fluid findings were improving. The duration of penicillin therapy in the 13 patients who recovered was as follows: 1 patient, 6 days; 3 patients, 7 days; 1 patient, 9 days; 1 patient, 10 days; 1 patient, 12 days; 3 patients, 13 days; 1 patient, 16 days and 2 patients, 17 days.

TABLE 2. RESULTS OF TREATMENT ACCORDING TO AGE

	Patients Treated with Penicillin Systemically and by Multiple Intrathecal Injections		Patients Treated with Massive Doses of Penicillin Systemically	
	Total	Died	Total	Died
0— 1 Yr.	4	3	3	3
1— 5 Yrs.	2	0	2	0
6—10 Yrs.	0	0	0	0
11—20 Yrs.	4	1	0	0
21—30 Yrs.	3	2	0	0
31—40 Yrs.	11	7	4	1
41—50 Yrs.	17	11	4	1
51—60 Yrs.	10	6	5	3
61—70 Yrs.	11	8	1	0
71—— Yrs.	4	3	2	0
	66	41 (62%)	21	8 (38%)

The effects of treatment can best be evaluated by comparing these patients with the 66 patients who have been treated by us with multiple intrathecal doses of penicillin. All except 5 were given systemic penicillin concomitantly in doses which varied from 120,000 units to 3,000,000 units per day. All except 3 of these patients received full doses of sulfonamides systemically in addition. The 2 groups were quite similar in all respects. As shown in Table 2, both series contained a large number of patients who were in age groups where the prognosis is unfavorable. The proportion of patients under 1 year of age

or over 40 years was 70% and 71% for the "multiple intrathecal series" and the "massive systemic series" respectively. From Table 3 it will be seen that the source of the infection was approximately the same in both series.

Results. Among the 21 patients treated with massive doses of penicillin systemically, 8, or 38%, died. This may be contrasted to 41 deaths among the 66 patients who received multiple intrathecal injections, a case fatality rate of 62%. These differences are not quite statistically significant when tested with the Yates modification of the Chi square method. Nevertheless, there are other factors which make it appear that the use of massive systemic doses is superior. If the patients who died within the first 24 hours of the start of penicillin therapy are excluded, 2 among 15 patients receiving massive systemic doses died (13%), and 33 among 58 receiving multiple intrathecal injections (57%). This difference is statistically significant.

Among the patients who recovered, the patients who received the massive doses of penicillin systemically had a more rapid drop in temperature. As shown in Figure 1, the temperature was below 101° F. in 12 of the 13 patients by the 7th day after the start of treatment. The 1 patient who had fever above this point for 21 days also had azotemia. He died 12 days after the temperature fell and 32 days after the start of treatment and was found at necropsy to have a malignant tumor of the left kidney with bony metastasis and no meningitis. The median day on which the temperature fell below 101° F. was the second day of treatment. In the same figure, the time of temperature fall has been charted for the last 19 patients who recovered in the series of patients who received multiple intrathecal injections. Although the temperature fell rapidly in the case of some patients, in half it took 2 weeks or longer to drop below 101° F. The median for this group was 8 days.

One disturbing factor in the treatment of meningitis with frequent intrathecal injections has been a prolonged duration of pleocytosis. The arbitrary level of cerebrospinal fluid leukocytes which we have used as a criterion for discharging the patient has been 30 per cubic millimeter or below, provided that all of the cells are lymphocytes. In Figure 2 are shown the days on which the cells first reached this level. Among the patients treated with massive systemic doses the duration of pleocytosis extended from 4 to 32 days, with a median of 8 days. It is interesting that the patient who continued to have an increased spinal fluid leukocyte count for 32 days was the one patient in the recovered group

TABLE 3. RESULTS OF TREATMENT ACCORDING TO SOURCE OF INFECTION

	Patients Treated with Penicillin Systemically and by Multiple Intrathecal Injections		Patients Treated with Massive Doses of Penicillin Systemically	
	Total	Died	Total	Died
Pneumonia	23	16	5	2
Otis and/or Mastoiditis	14	5	2	0
Endocarditis	2	2	2	2
Head Injury	1	0	1	0
Source not determined	26	18	11	4
	66	41	21	8

who received a single intrathecal injection at the beginning of therapy. The duration of pleocytosis was definitely longer in the group of patients who received multiple intrathecal injections, extending from 6 to 103 days with a median of 20 days.

No untoward reactions have been observed in the 21 patients receiving 12,000,000 units of penicillin every 24 hours for meningitis, nor in 20 other patients to whom we have given the same or higher doses for other types of infections.

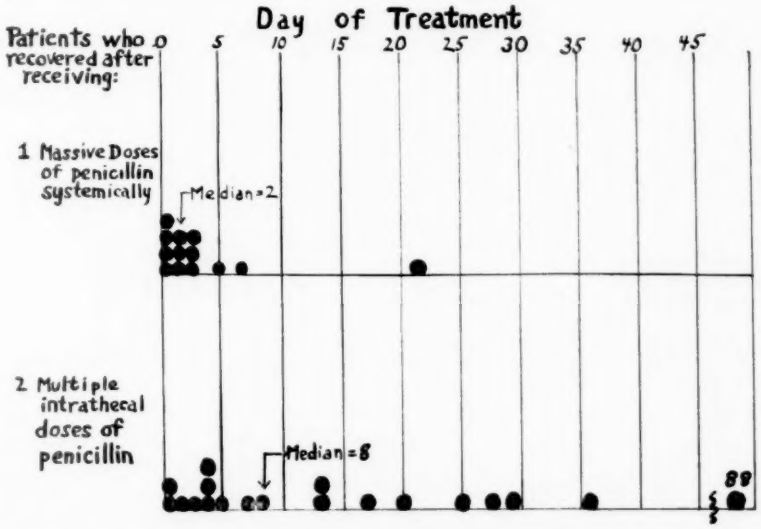

Figure 1—Day on which the temperature fell below 101° F in the patients who recovered.

Discussion. Pneumococcic meningitis has been treated by means of systemic penicillin without intrathecal therapy in a few instances. Price and Hodges[25] gave doses of 48,000 to 100,000 units per day intramuscularly or by continuous intravenous injection to 3 patients. Two patients, aged 3 months and 36 years, recovered. The other patient, aged 54 years, died. White and his co-workers[38] treated 7 patients, of whom 4 died. Systemic doses did not exceed 200,000 units per day. Lawson and Kelsey[18] gave 15,000 to 20,000 units of penicillin per pound of body weight to 2 infants along with a single intrathecal dose of penicillin. Both recovered. It will be noted that all of these patients, with the possible exception of the last 2, were treated with rather small doses of penicillin. The concentration of penicillin which one would expect to find in the cerebrospinal fluid in these patients would be low if the antibiotic was present at all. Whether penicillin must be present in the cerebrospinal fluid to cure pneumococcic and other infections, so long as it is present in the tissues of the central nervous system, is a debatable point. The presence of penicillin in high concentrations in the cerebrospinal fluid, however, makes it likely that it is present also in the adjacent nerve tissue. With the dose of penicillin which we employed, relatively high concentrations of penicillin are assured at all times after the first few hours. Further investigation is necessary to determine whether the concentration could be increased more rapidly. Pos-

sibly this might be accomplished by giving an initial intravenous injection of 1,000,000 units over the course of 3 or 4 hours. Until a suitable method is devised for this purpose, it may be the wisest policy to give a single initial intrathecal injection of 20,000 units of penicillin as soon as the diagnosis of pneumococcic meningitis is made, to all patients in coma and others who appear to be in extremis. In the other patients we believe it is advisable to refrain from giving intrathecal penicillin, since even a single dose may increase the duration of pleocytosis and damage in the form of subarachnoid adhesions.

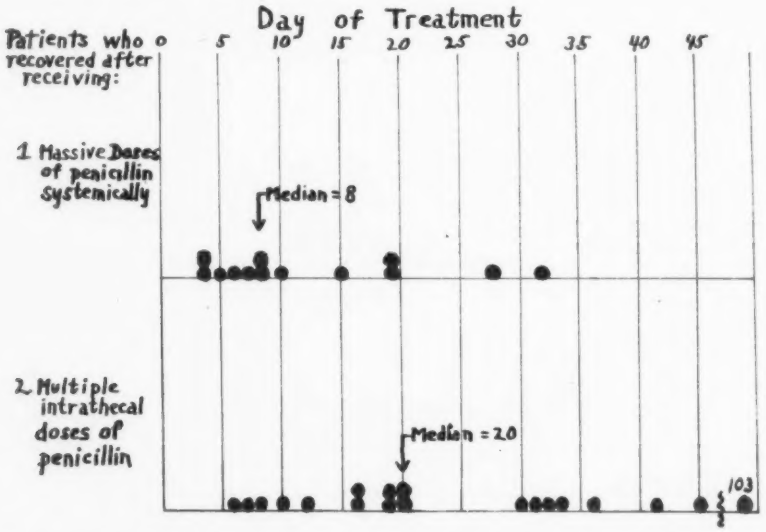

Figure 2—Day on which the cerebrospinal fluid leukocyte count fell to 30 per cubic millimeter or below, in the patients who recovered.

This method of therapy may be applicable to other types of purulent meningitis such as the staphylococcic and streptococcic varities. We have had an opportunity to use this regimen in only 1 infant with meningitis caused by the hemolytic streptococcus. The patient recovered. The good results obtained in pneumococcic meningitis may also justify a re-evaluation of the possibility of employing similar large doses in infections in serous cavities where diffusion is inadequate with the doses of penicillin ordinarily used.

Sulfonamides do not appear to have any value as adjuvants when these large doses of penicillin are used. Sulfonamides were given to 13 of our patients, 7 of whom died. The main reason for employing these drugs in conjunction with penicillin, namely, that they diffuse so well into the cerebrospinal fluid, apparently has no significance when doses of penicillin are employed which insure the proper diffusion of the antibiotic.

Summary and Conclusions. 1. Twenty-one patients with pneumococcic meningitis have been treated with 1,000,000 units of penicillin intramuscularly every 2 hours. Three of them received a single intrathecal injection of penicillin: the others were given no intrathecal therapy. Thirteen patients received sulfonamides in addition. There were 8 deaths, a case fatality

rate of 38%, compared with 41 deaths (62%) among the 66 patients previously treated by us with smaller doses of penicillin systemically plus repeated intrathecal injections of penicillin.

2. In the patients who recovered, the temperature dropped more rapidly among those who received massive systemic doses than among those who were given repeated intrathecal injections. Likewise the duration of pleocytosis was shorter in the former group.

3. Since the results of massive systemic penicillin therapy in pneumococcic meningitis are at least as good and apparently better than those obtained with the conventional systemic doses of penicillin plus multiple intrathecal doses, it is recommended that all patients with pneumococcic meningitis be given 1,000,000 units of penicillin intramuscularly at 2 hour intervals. Patients in coma or in extremis when treatment is begun may be given a single initial intrathecal dose of penicillin in addition. Sulfonamides do not appear to be necessary when these doses are used.

We wish to thank Mrs. Joan R. Broyhill and Miss Myrtle Meyer for technical assistance.

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PENICILLIN SYPHILOTHERAPY ADMINISTERED DURING PREGNANCY
A STUDY OF 149 PREGNANCIES DURING WHICH PENICILLIN WAS GIVEN FOR EARLY MATERNAL SYPHILIS

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Most workers in the field regard penicillin as the treatment of choice for the syphilitic pregnant woman because of its lack of toxicity, the high proportion of satisfactory results obtained, and the brevity of treatment.[1,2,3,4,7,8,10,11,12] It has been recommended that in this situation the older methods of therapy be abandoned. Our experience has grown since 1946[4] to include 149 women with early syphilis who have been treated with penicillin during pregnancy. It is the purpose of this brief paper to present the results obtained, in terms of maternal and fetal outcome, and to emphasize further the desirability of penicillin treatment for the syphilitic pregnant woman.

Material and Methods. Between October, 1943, and March, 1948, 149 women were treated with penicillin for concomitant early syphilis and pregnancy in the Johns Hopkins Hospital.† Twenty-three of these were white; 126 (85.6%) were Negresses. The original diagnosis in 70 patients (47.0%) was primary and/or secondary syphilis. In the majority of these *Treponema pallida* were demonstrated under the darkfield microscope. The remainder had early latent or early asymptomatic neurosyphilis of less than 2 years' duration.

As soon as the diagnosis of concomitant pregnancy and untreated early syphilis was established, each woman was given treatment with penicillin. In several, especially early in the study when comparatively small total amounts of penicillin were administered (that is, less than 3 million units), mapharsen (approximately 300 mg.) and bismuth (approximately 600 mg.) were given concurrently. When treatment had been completed, each patient was followed monthly in a special prenatal clinic. Complete examination of the skin and mucous membranes and quantitative serologic evaluation were carried out at each visit, in addition to routine prenatal care. In the event lesions of mucocutaneous relapse (or reinfection) were encountered, if the titer remained at a high level after treatment (seroresistance), or showed a marked and sustained rise (serorelapse), retreatment with penicillin was instituted immediately. After retreatment, the monthly clinic visits were resumed.

Offspring of these mothers were followed at monthly intervals for from 4 months to a year or longer in the Family Syphilis Clinic of the Johns Hopkins Hospital with titered serologic tests and complete physical examinations. Roentgenograms of the long bones were obtained one or more times in approximately one-third of these babies.

Maternal syphilotherapy, for the majority of these patients, consisted of amorphous or crystalline penicillin G only; 40% received the latter preparation. No difference in outcome in the 2 groups was noted. Although all women requiring retreatment had originally been given amorphous penicillin, such "treatment failures" were attributed more to the comparatively small total doses these women received than to the penicillin preparation itself. In Table 1 are presented the amounts of antibiotic administered to these women in relation to the month of gestation when therapy was begun.‡ In all patients treated during pregnancy the antibiotic was given in aqueous solution, intramuscularly, at intervals of every 2 or 3 hours over a period of 7.5 to 15 days on an in-patient basis.

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†Of these, 34 have since been followed through one or more subsequent pregnancies without additional syphilotherapy and have been described in a separate communication.[13]

‡ Women requiring retreatment were entered in the Tables according to the total amount of penicillin received during pregnancy and month of gestation the last course of penicillin was administered.

Results. The outcome of each of the 149 pregnancies is tabulated in Table 2. Congenital syphilis was found in none. The single neonatal death, due to sickle cell anemia, occurred in a full-term Negro infant. One abortion took place in the 15th week of pregnancy, the other 4.5 months after conception. In neither was there evidence of syphilis and both mothers had completed syphilotherapy prior to these disasters. These women, as well as the mothers of 10 of the premature infants, were patient had been given 9.6 million units of amorphous penicillin in peanut oil-beeswax; serorelapses during pregnancy required 4.8 and 6.1 million units of penicillin G in the 2nd and 9th months of pregnancy, respectively. Two other women, following 0.6 and 2.4 million units of amorphous penicillin in the 2nd and 4th months of gestation, underwent serorelapse and required 1.2 and 3.1 million units of additional amorphous penicillin during the 5th and 9th months, respectively. In all other

TABLE 1.—PENICILLIN SYPHILOTHERAPY GIVEN TO 149 WOMEN, BY MONTH OF GESTATION DURING WHICH TREATMENT WAS STARTED.

Total amount penicillin administered (millions of units)	Number of patients	Month of gestation								
		1	2	3	4	5	6	7	8	9
0.6 to 1.0	1	–	–	–	1			–	–	–
1.0 to 2.0	19	2	1	3	4	4	1	2	2	–
2.0 to 3.0	25	–	1	3	1	3	8	4	2	3
3.0 to 4.0	8	1	2	–	2	–		1	1	1
4.0 to 5.0	91	–	3	5	9	17	20	15	12	10
> 5.0	5	–	–	1	–	1	–	–		3
Total	149	3	7	12	17	25	29	22	17	17

originally treated for primary and, or, secondary syphilis. In none of the 16 infants born prematurely could either maternal disease or penicillin therapy be incriminated as the cause of prematurity. The incidence of prematurity in this study (10.7%) probably did not differ significantly from the expected incidence in a similar but non-syphilitic group of mothers[1].

Indication for retreatment arose in 6 pregnant women (4%). Two women originally treated prior to these pregnancies with 3.6 and 0.8 million Oxford units, underwent serorelapse. Retreatment with 3.6 million units of amorphous penicillin during the 5th and 7th months of pregnancy, respectively, effectively prevented (or cured) congenital syphilis in the offspring. Another woman, treated prior to pregnancy with 2.4 million units, required retreatment with 4.8 million units of penicillin G because of infectious relapse (reinfection ?) during the 3rd month of gestation. One non-pregnant patients, the intensive routine of prenatal examinations did not disclose indications for retreatment.

Data concerning the maternal titer and the serologic titer of the infant's cord blood were available in 67 records. In 24 of these the mother was seropositive, the cord blood negative; the maternal titer was, as a rule, in the range of 1 to 8 Eagle units. In 30 records the maternal and cord blood determinations were both positive. In 2 of these the maternal and infantile titers were identical but in the remainder the cord blood titers were lower than the maternal ones, which tended to be in the range of 4 to 16 Eagle units or higher. Twelve mothers who were seronegative had seronegative babies and in a single instance such a mother had a seropositive baby. Repetition of this infant's serologic test in the first week of life yielded a negative test which was repeatedly confirmed thereafter. These resembled data reported by others[2,10,12].

Of those born alive, 48 infants (32.6%) were seropositive in the cord blood or at the time of the first visit to the Family Syphilis Clinic. In many of these it was impossible to tell when reversion to negative took place, within wide limits, because of long intervals between examinations. Two, however, were seropositive when tested between 71 and 80 days after birth and reverted during the next 10-day period. The most persistent seropositivity was exhibited by a Negro baby whose mother (treated during the 5th month of pregnancy) had a titer of 32 Eagle units at the time of delivery; the cord blood was positive in a titer of 8 units. Nine subsequent serologic tests were positive, in gradually falling titer, the last one being obtained 101 days after birth. When next examined, 20 days later, he was seronegative. Several roentgenograms of the long bones were normal and he has remained clinically well throughout the first year of life. Every survivor in this group of infants born of penicillin-treated mothers with early syphilis had become seronegative by the end of the 4th month of life.

One or more roentgenograms of the long bones were taken in 54 infants. In the majority of these (77.8%) the osseous structures were described as normal. In 12 infants, however, changes compatible with osseous congenital syphilis were noted. These findings were interpreted by us as healing or regressing lesions and were considered evidence that *in utero* infection had probably occurred in these babies, but that the penicillin administered to the mother had effected cure of the fetal disease. These data, together with the unusual serologic findings mentioned previously, will be elaborated in a later communication[5].

Discussion. Data obtained in this study support strongly the belief that penicillin is the treatment of choice for the syphilitic pregnant woman. These results, obtained in women with syphilis of less than 2 years' duration are entirely applicable to those with late syphilis[4]. Since penicillin, like arsenic and bismuth, has been repeatedly shown to penetrate the placental barrier at any time after the 10th week of gestation, it is reasonable to assume that the antibiotic, administered to the mother may function either to prevent transmission of the disease to the fetus or to effect cure of the fetus once congenital syphilis has been established[12]. Three lines of evidence support the contention that the fetal disease may be cured as well as prevented:

It made no difference when in pregnancy penicillin was administered (see Table I), in so far as the incidence of infantile congenital syphilis was concerned[8]. In this study, 73.4% of the patients were treated during or after the 5th month of gestation. Although these fetuses may have been infected, syphilotherapy after birth was necessary in none.

The second observation showing that

TABLE 2.—CLASSIFICATION OF PROGENY OF 149 MOTHERS, BY AMOUNT OF PENICILLIN SYPHILOTHERAPY GIVEN DURING PREGNANCY.

Total amount penicillin administered (millions of units)	Non-syphilitic				Syphilitic
	Full term	Premature	Abortion	Neonatal death	
0.6 to 1.0	1	–	–	–	–
1.0 to 2.0	13	3	2	1	–
2.0 to 3.0	23	2	–	–	–
3.0 to 4.0	6	2	–	–	–
4.0 to 5.0	84*	8	–	–	–
> 5.0	4	1	–	–	–
Total	131	16	2	1	0

*Including one set of twins

in utero disease may be attacked by maternal penicillin treatment, was that infants born of 12 mothers (all treated during or after the 5th month) had radiographic changes compatible with the residuals of osseous congenital syphilis[6]. All remained clinically well in the absence of syphilotherapy, and all became seronegative within the first 4 months of life.

The third factor was that several of the infants exhibited a marked persistence of reagin. This phenomenon has recently been encountered by other workers[12]. Ordinarily, "the maximum length of time for which maternal reagin has been observed to persist in the blood of a normal infant is 70 days"[9]. In this series 2 infants were shown to undergo seroreversal between 81 and 90 days of life, and one between 101 and 121 days. This was interpreted by us as probably being due to additional reagin actively elaborated by these fetuses as a consequence of congenital syphilitic infection. Such infants would be analogous to adults treated for early acquired syphilis who usually require 6 months or longer to achieve seronegativity after adequate syphilotherapy.

Within wide limits, the total amount of antibiotic administered to the women in this series, or whether crystalline penicillin G was employed, did not appear to influence materially the outcome of pregnancy. On the other hand, no patient who was given 4 million units or more required retreatment. It is our feeling, therefore, that a total amount of penicillin of 4.8 million units or more, without supplementary metal chemotherapy, is entirely adequate for the treatment of early (or late) syphilis in the mother, the prevention of transmission of syphilis to the uninfected fetus, and the cure of congenital syphilis in the fetus if infection has already taken place. This statement implies concentrated prenatal and post-partum follow-up care.

Relapse or reinfection may occur at any time and intensive follow-up routines should be adhered to in order to eliminate effectively congenital syphilis. Even though healthy babies may be born of mothers treated late in pregnancy, the presence of *T. pallida* in the fetuses for one or more months can do nothing but harm. Therapy should be instituted at the earliest possible moment after the discovery of relapse or reinfection in the pregnant woman. By prompt retreatment, damage to the fetus should be minimized.

Summary. Between 1943 and March, 1948, 149 women with concomitant early syphilis and pregnancy were treated with penicillin at the Johns Hopkins Hospital in total amounts ranging from 0.6 to over 5 million Oxford units. In all cases the antibiotic was given in aqueous solution, intramuscularly, every 2 or 3 hours for 7.5 to 15 days. Six women (4%) required retreatment with penicillin for relapse or reinfection, seroresistance, or serorelapse. Nearly three-quarters of all patients were treated after the 4th month of gestation.

Two abortions occurred; in neither could syphilis or maternal penicillin administration be implicated. Sixteen infants were premature but survived. The remainder were full-term infants, one of whom died of sickle cell anemia during the neonatal period. On the basis of clinical, serologic, and, or, roentgenologic evidence through the first 4 months of life or longer, treatment for infantile congenital syphilis was indicated in none.

These data furnished additional evidence that penicillin, combined with intensive post-treatment serologic and clinical study, is the current treatment of choice for the syphilitic pregnant woman.

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NITROGEN MUSTARD THERAPY

The Use of Methyl Bis (B Chloroethyl) Amine Hydrochloride in Hodgkin's Disease, Leukemia, Lymphosarcoma and Cancer of the Lung

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The first clinical trial of a nitrogen mustard as a therapeutic agent in the treatment of neoplastic diseases was made by Gilman, Goodman, Lindskog and Dougherty[1] in 1942. These investigators administered tris (β chloroethyl) amine hydrochloride intravenously to 6 patients in the terminal stages of various neoplastic diseases. In 2 patients with lymphosarcoma, the drug caused a rapid dissolution of large tumor masses. These gratifying results led to the further clinical investigation of this drug and also of methyl bis (β chloroethyl) amine hydrochloride in neoplasms involving the lymphoid and hemopoietic tissues.[2,3,4,5]

This paper is concerned with the use of methyl bis (β chloroethyl) amine hydrochloride in cases of Hodgkin's disease, leukemia, lymphosarcoma and carcinoma of the lung. Eleven of these cases are included in a report which will be published by the National Research Council. In this communication observation on the use of the drug in 29 additional patients will be reported.

Method. Methyl bis (β chloroethyl) amine hydrochloride was administered intravenously at a daily dose of .1 mg. per kg. of body weight. A course of treatment consisted of 4 consecutive daily injections. When marked changes in the blood were noted, the course was interrupted and subsequent injections were given at intervals of 2 to 4 days. The solution was freshly made by injecting 10 cc. of a sterile isotonic solution of sodium chloride in a vial containing 10 mg. of the drug. The injection was given immediately after the solution was prepared. In a few patients the injection was given directly into a vein with a syringe. In the majority of the patients the solution was injected with a rubber tubing during a course of saline infusion. Special care was taken to prevent extravasation of the solution and prolonged contact with the skin. Additional courses were given at 2 to 16 week intervals depending upon the response to the nitrogen mustard and the hematological effect. Complete blood counts were made before treatment and at frequent intervals after the injection. In selected patients repeated sternal marrow aspirations were performed.

Results. The pertinent data of each patient treated are tabulated in Table 1. A summary of the results of treatment in each group is given in Table 2.

Hodgkin's Disease: Thirteen patients with this disease were treated with nitrogen mustard; 11 had previously had Roentgen-ray therapy. In 11 of the 13 patients, the drug produced remissions lasting from 6 weeks to 19 months. Seven of the 11 patients were taken to be Roentgen-ray resistant. In these 11 patients, a course of nitrogen mustard resulted in a moderate to marked general improvement in health. The temperature was lowered or became normal, the appetite improved, the lymph nodes regressed, and pruritus diminished. In 3 patients the liver and spleen became smaller and in 2 patients the amount of involvement of lung parenchyma was reduced. The response was estimated as good in 6 and fair in 5 patients. One patient (Case 2) had Hodgkin's disease for 8

TABLE 1. SUMMARY OF PATIENTS TREATED WITH NITROGEN MUSTARD

Case	Name	Age	Sex	Duration of disease before HN_2HCL therapy (mos.)	Previous therapy	Condition of patient before therapy	No. of courses given**	Duration of remission (range in mos.)	General response	Comments
HODGKIN'S DISEASE										
1*	R.G.	31	F	24	x-ray	poor	3.25	1.5–2	fair	Died 9 mos. after initiation of treatment.
2*	N.B.	41	M	96	x-ray	poor	1	19	good	Continues in remission; returned to his occupation.
3*	G.K.	37	F	14	x-ray	fair	2	3–11	good	Continues in remission of 11 mos.; returned to her occupation.
4*	B.W.	46	M	84	None	fair	1	12	good	Continues in remission; returned to his occupation.
5	L.K.	42	M	30	x-ray	poor	4	2–6	fair	Died 10 mos. after initiation of treatment.
6	G.S.	38	F	25	x-ray	fair	2	4–7	fair	Continues in remission of 4 mos.
7	S.R.	44	M	36	x-ray	poor	3	1–3	fair	Continues in remission of 3 mos.
8	C.M.	39	F	48	x-ray	poor	1	None	poor	Died 6 wks. after initiation of treatment.
9	H.B.	53	M	21	x-ray	fair	2	3–5	good	Continues in remission of 5 mos.; returned to his occupation.
10	K.L.	25	F	5	None	poor	2	1–3	good	Continues in remission of 3 mos.; returned to her occupation.
11	L.B.	44	F	10	x-ray	poor	2	2–6	good	Continues in remission of 6 mos.
12	G.F.	48	M	18	x-ray	fair	1	3	fair	Continues in remission.
13	F.K.	49	M	60	x-ray	poor	1	—	poor	Died 1 mo. after initiation of treatment.
CHRONIC LYMPHATIC LEUKEMIA										
14	H.F.	54	M	21	x-ray	fair	2	3	fair	Failed to respond to a 2nd course; died 6 mos. after initiation of treatment.
15	D.G.	42	F	8	None	fair	1	7	good	Continues in remission.
16	A.M.	50	M	60	x-ray	poor	2	—	poor	Died 4 mos. after initiation of treatment.
17	S.J.	48	F	36	x-ray	fair	2	1.5	fair	Failed to respond to a 2nd course; died 4 mos. after initiation of treatment.
18	B.G.	66	M	42	x-ray	poor	1	—	poor	Patient still living; condition is poor.
ACUTE LYMPHATIC LEUKEMIA										
19	S.L.	42	M	2	None	poor	1	—	poor	Died 1 mo. after initiation of treatment.
CHRONIC MYELOGENOUS LEUKEMIA										
20*	E.H.	33	F	40	x-ray radio-active phosphorus	poor	1	None	poor	Died 2 mos. after initiation of treatment.
21	A.R.	31	M	36	x-ray	poor	2	1.5	fair	Failed to respond to a 2nd course of HN_2HCL; died 3 mos. after initiation of treatment.
22	B.J.	56	F	18	None	fair	1	None	poor	Patient is now receiving x-ray therapy.
23	H.S.	38	M	24	None	poor	2	2–3	fair	Continues in remission of 3 mos.
24	A.F.	40	F	53	x-ray	poor	3	None	poor	Died 2 mos. after initiation of treatment.
LYMPHOSARCOMA										
25	B.L.	40	M	20	x-ray	poor	2	—	poor	Died 2 mos. after initiation of treatment.
26	M.W.	18	F	6	None	fair	1	5	good	Continues in remission.
27	H.R.	63	M	15	x-ray	poor	2	—	poor	Died 4 mos. after initiation of treatment.
28	L.P.	28	M	12	x-ray	fair	1	3	good	Continues in remission.
29	F.G.	31	F	18	x-ray	poor	1	—	poor	Died 3 mos. after initiation of treatment.
CARCINOMA OF THE LUNG (SQUAMOUS CELL)										
30*	B.P.	65	M	10	None	fair	2	—	poor	Died 8 mos. after initiation of treatment.
31*	G.G.	47	M	8	None	fair	2	1.5	fair	Failed to respond to a 2nd course; died 7 mos. after initiation of treatment.
32*	A.H.	71	M	12	x-ray	poor	1	—	poor	Died 4 mos. after initiation of treatment.
33*	M.K.	55	F	18	None	poor	1	—	poor	Died 2 mos. after initiation of treatment.
34	H.T.	48	M	6	x-ray	fair	1	—	poor	Patient is still living; condition is poor.
35	F.M.	60	M	15	x-ray	fair	2	—	poor	Died 1 mo. after initiation of treatment.
36	A.C.	48	M	4	None	fair	1	—	poor	Patient now receiving x-ray therapy.
CARCINOMA OF THE LUNG (ANAPLASTIC)										
37*	S.W.	54	M	6	None	poor	2	3	good	Failed to respond to a 2nd course; died 5 mos. after initiation of treatment.
38*	H.N.	73	F	11	x-ray	poor	1	—	poor	Died 2 mos. after initiation of treatment.
39	F.O.	50	M	6	x-ray	fair	2	—	poor	Patient is still living; condition is poor.
40	G.D.	42	M	7	x-ray	poor	1	—	poor	Patient is still living; condition is poor.

* Included in report to be published by the National Research Council
** Course = 4 injections of 0.1 mg. per kg. for 4 doses

TABLE 2. SUMMARY OF RESULTS OF TREATMENT WITH NITROGEN MUSTARD

	Hodgkin's Disease	*Leukemia Lymphatic*	*Leukemia Myelogenous*	*Lympho-sarcoma*	*Cancer of the Lung*
Total No. of Cases	13	6	5	5	11
Male	7	4	2	3	10
Female	6	2	3	2	1
Average Age (yrs.)	42	50	39.6	36	55.7
Range	25–58	42–66	31–56	18–63	42–73
Average Duration of Disease (mos.)	36	28.2	34.2	14.2	9.4
Range	5–96	2–60	18–53	6–20	4–18
No. Previously Treated with x-rays	11	4	3*	4	6
No. Initially Treated with HN_2HCL	2	2	2	1	5
No. of Courses Given (Range)	1–4	1–2	1–3	1–2	1–3
Results					
Good	6	1	None	2	None
Fair	5	2	2	None	2
Poor	2	3	3	3	10
Average Duration of Remission (mos.)	4.8	3.8	2.1	4	2.2
Range	1.5–19	1.5–7	1.5–3	3–5	1.5–3
No. of Patients Living Since HN_2HCL was Started	9	2	2	2	4
No. of Mos. Living Since HN_2HCL was Started	3–18	2–7	1–3	3–5	2–4
No. of Patients Dead Since HN_2HCL was Started	4	4	3	3	7
Duration of Life Since HN_2HCL was Started (mos.)	1–8	1–4	2–3	2–4	1–7

* One patient received radio-active phosphorus in addition to x-rays.

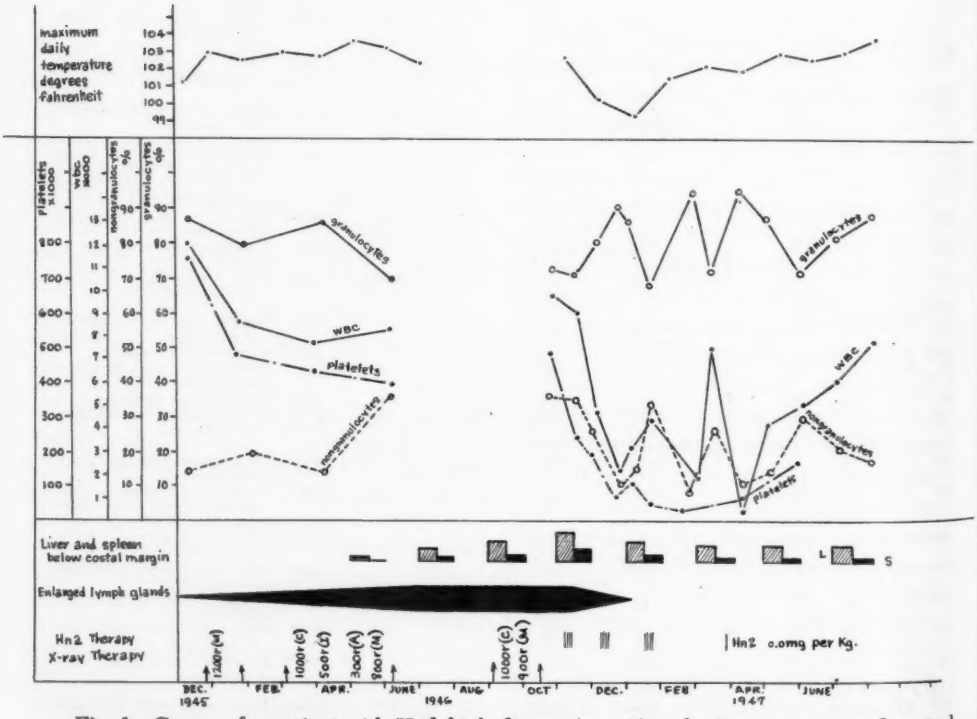

Fig. 1.—Course of a patient with Hodgkin's disease (case 1) under Roentgen-ray and mustard therapy. (M) = mediastinum; (C) = cervical; (I) = inguinal; (A) = axillary.

years and no longer responded to Roentgen-ray therapy. Before nitrogen mustard was given, this patient was an invalid because of paraplegia. One month after a course of nitrogen mustard the patient was able to return to his occupation. He is now in a remission which has lasted 19 months. Two patients who were treated in the late stages of the disease did not respond to nitrogen mustard. Two of the 11 patients who showed a response died of an extension of the disease within 9 to 10 months after nitrogen mustard therapy was begun. Five of the 11 patients are now able to carry on their occupations.

The following case history, although it does not represent the best results obtained from nitrogen mustard, is given because it illustrates the comparative effects of this drug and those of Roentgen rays in a patient with a virulent type of Hodgkin's disease.

Case History: Case 1. R. G., a 30 year old female was admitted to the Greenville Hospital on December 10, 1945, with the chief complaint of pruritus, cough, fever and weakness. One year prior to admission, the patient developed a generalized pruritus and felt weak. Ten months before admission, she began to have a fever for which she was given sulfa drugs. The fever, however, persisted and the pruritus increased in intensity until admission to the hospital.

Physical examination disclosed areas of pigmentation over the body and the extremities. A very small lymph node was felt in the right supraclavicular region. There was flatness to percussion below the angle of the right scapular. Vocal fremitus was absent over that area and the breath sounds were diminished. The heart was displaced to the left. The temperature was 102.2° and the pulse rate was 112.

The urine was normal.

A blood count showed hemoglobin 74%, red blood cells 4,200,000, white blood cells 11,400 (neutrophils 84%; lymphocytes 8%; monocytes 6%; eosinophils 1% and myelocytes 1%). The platelet count was 780,000 per cu. mm. A chest plate showed a homogeneous density extending from the level of the 3rd rib to the base. Thoracentesis resulted in the removal of 1000 cc. of clear yellow fluid. A biopsy of the right supraclavicular gland showed Hodgkin's disease.

Radiation therapy was given during the period of December 20, 1945 to October 14, 1946 (Fig. 1). Following a course of 1200r to the mediastinum, the patient felt much worse. The cervical, axillary and inguinal glands became enlarged and the temperature was higher. She was then given 1000r to the right and left cervical regions, 500r to the right and left inguinal regions, 300r to the right and left axillary regions, and 800r to the mediastinum. The response was poor. In May, 1947, the liver and spleen became palpable. She received another course of 1000r to the right and left cervical regions and 900r to the mediastinum. The liver and spleen gradually became larger and the patient developed ascites and edema of the lower extremities.

Nitrogen mustard therapy was initiated on November 7, 1946. Methyl bis (β chloroethyl) amine hydrochloride, .1 mg. per kg. of body weight, was injected intravenously by the direct route for 4 consecutive days. Nausea and vomiting occurred 2 hours after the injection and lasted for 4 hours. Three days after the course was completed the temperature was lower and the appetite was improved. The peripheral glands began to regress. Another course of nitrogen mustard was given during the period of December 4 to December 7, 1946, inclusive. Following the second course, the temperature became normal and the enlarged lymph glands disappeared. The liver and spleen became smaller and the patient felt improved. The white count fell gradually and on December 10 there were 2050 leukocytes per cu. mm. The platelet count fell to 79,000 per cu. mm. One week later the leukocytes rose to 3100 per cu. mm. and the platelet count to 124,000 per cu. mm. In January 1947, the temperature began to rise again and the pruritus increased in intensity. A third course of nitrogen mustard was

started on January 17, 1947, and was given for 4 consecutive days. The response was fair and a remission was produced which lasted for 6 weeks. On March 21, 1947, she was given one injection of nitrogen mustard. The next day the leukocyte count fell to 300 per cu. mm. and the platelet count fell to 40,000 per cu. mm. There were 92% granulocytes and 8% nongranulocytes. Nitrogen mustard was then discontinued. The temperature remained high and the patient became confined to bed. There was, however, no lymphadenopathy. On April 14, the leukocyte count rose to 3850 per cu. mm. and the differential count showed 85% granulocytes and 15% lymphocytes. On April 18, a platelet count showed 120,000 per cu. mm. In May, 1947, hirsuties became a prominent feature. The patient became markedly cachectic, ran a downhill course and died July 29, 1947.

Autopsy showed diffuse involvement of the lungs, mediastinum, pericardium, pleura and pelvic organs by granulomatous tissue. The mesentery and omentum were also involved. The right lung was almost completely replaced by granulomatous tissue. The heart was small and showed invasion of the right atrium. The liver and spleen showed focal involvement. The inferior vena cava was obstructed by granulomatous tissue. Microscopic examination showed Hodgkin's disease. There was considerable variation in histologic structure ranging from granulomatous to sarcomatoid lesions.

Comment. This patient, with a severe form of Hodgkin's disease, became worse after Roentgen-ray therapy was started. Diffuse enlargement of the peripheral glands, absent before treatment, became a prominent feature after the first course of Roentgen rays was completed. Nitrogen mustard produced temporary remissions and a dissolution of the enlarged glands.

Leukemia: Six patients with lymphatic leukemia were treated with nitrogen mustard; 5 had the chronic type and 1 the acute type of the disease. Four of the 6 were previously treated with Roentgen rays. In 3 patients remissions were produced varying from 6 weeks to 7 months in duration. The response was good in 1 and fair in 2 patients. One patient with chronic lymphatic leukemia remains in a remission of 7 months after one course of nitrogen mustard. Two other patients with the same type of disease obtained remissions of 6 weeks to 3 months. These 2 patients did not respond to a second course and died within 4 to 6 months after nitrogen mustard was begun. Two patients with the chronic type and 1 with the acute type of lymphatic leukemia did not respond to nitrogen mustard.

Five patients with chronic myelogenous leukemia received nitrogen mustard therapy. Three of these were previously treated with Roentgen rays; 1 patient also received radio-active phosphorous in addition to Roentgen rays. In 2 of the 5 the response was fair. One patient had a remission of 6 weeks and failed to respond to a second course of nitrogen mustard; this patient died 3 months after nitrogen mustard was begun. Another patient had a remission of 2 months following the initial course and remains in a remission 3 months following a second course of nitrogen mustard. Three patients with chronic myelogenous leukemia did not respond to nitrogen mustard.

Lymphosarcoma: Of the 5 patients with this disease treated with nitrogen mustard, all except one had previously had Roentgen-ray therapy. In 2 patients the response was good. One course of nitrogen mustard produced in these patients remissions of 3 to 5 months. The remissions consisted of a feeling of general well-being, a gain in weight, and a dissolution of the enlarged lymph glands. Three patients with lymphosarcoma did not respond to nitrogen mustard and died within 2 to 4 months after the drug was given.

Carcinoma of the Lung: Eleven patients with carcinoma of the lung were treated with nitrogen mustard. In 7 patients the pathological diagnosis was squamous cell carcinoma, in 4 patients it was anaplastic carcinoma. One patient (Case 37) with anaplastic carcinoma had considerable relief of a superior vena cava compression syndrome for 3 months from 1 course of nitrogen mustard. He did not respond to a second course of nitrogen mustard and died 5 months after the drug was given. Another patient (Case 31) with squamous cell carcinoma had relief of chest pain, cough and hemoptysis for 6 weeks following a course of nitrogen mustard. This patient died 7 months after nitrogen mustard was given. Nine patients with carcinoma of the lung did not respond to nitrogen mustard.

Toxic Effects. *Nausea and Vomiting:* This was present in most patients treated with nitrogen mustard. It usually occurred within 2 to 6 hours after an injection and lasted for 3 to 12 hours. Some patients had nausea or vomited only after the first injection. The nausea and vomiting were often followed by a temporary improvement in appetite. This was also noted in those patients who showed no significant response to nitrogen mustard. Preliminary sedation was effective in alleviating the nausea and vomiting in a number of patients.

Venous Thrombosis: Thrombosis of the vein at the site of the injection occurred in the majority of the patients treated with nitrogen mustard by the direct route. This complication was largely eliminated when the drug was injected into a rubber tubing during an infusion of normal saline.

Hematological Effects: Changes in the blood were usually evident during the week following nitrogen mustard therapy. These consisted of a drop in the white blood cells associated with a reduction in the number of lymphocytes and granulocytes. A reduction in the number of platelets was also common. These changes usually lasted for 2 to 3 weeks. Leukopenic levels of 1000 white blood cells or less were noted in 4 patients and thrombocytopenia of 60,000 or less was found in 3 patients. Agranulocytosis and bleeding tendencies were not encountered. A slight reduction in the number of red cells and in the amount of hemoglobin was noted in a few patients. In some cases of Hodgkin's disease, an anemia that was present before treatment improved following a course of nitrogen mustard.

Summary and Conclusions. A group of 40 patients (Hodgkin's disease, 13 cases; leukemia, 11 cases; lymphosarcoma, 5 cases; and carcinoma of the lung, 11 cases) was treated with methyl bis (β chloroethyl) amine hydrochloride. Most of them were treated in the late stages of the disease and had had previous Roentgen-ray therapy.

In patients with Hodgkin's disease remissions were produced from one or more courses of nitrogen mustard. Dramatic results were observed in a few patients who were Roentgen-ray resistant. In patients with lymphatic leukemia, myelogenous leukemia and lymphosarcoma the results were not so encouraging. Although remissions of 3 to 5 months were observed in a few patients, the majority of the patients who showed a response were dead within 7 months after nitrogen mustard was first given. Nitrogen mustard did not appear to be of much value in the treatment of carcinoma of the lung.

The most important reaction to the use of this drug was its effect on the blood. This consisted of leukopenia, lymphopenia, granulocytopenia and thrombocytopenia. Recovery took place in 3 to 4 weeks. Instances of agranu-

locytosis and bleeding tendencies were not encountered.

From this study it is evident that nitrogen mustard may be of particular value in Hodgkin's disease. Its usefulness in leukemia, lymphosarcoma, and carcinoma of the lung remains to be evaluated.

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DEATH DURING SKIN TESTING

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Sudden death during diagnostic skin testing, it is believed, is sufficiently rare and disconcerting to warrant the report of another case. In our experience many physicians, who have not specialized in the practice of allergy, frequently employ diagnostic skin tests, and it is doubtful if many fully appreciate the hazards inherent in the procedure.

Anaphylactic shock and death in human beings has been reported from time to time, but the probability is that the number of such published reports inadequately reflects the real incidence of these episodes. Cook[6] in 1922 called attention to reports of violent reactions and sudden death that had been accumulated in the literature. Rosenau and Anderson[20] in 1906 reported 19 fatal cases; Gillette in 1909, 30 cases. Lamson[16] in 1924 reviewed the literature back to 1894, the year diphtheria antitoxin came into use. He found 41 incidences of anaphylactic death in human beings. Vaughan and Pipes[29] in 1936 added 22 cases, and Swineford[21] in 1946, 7 cases. It should be observed that the great majority of these accidents occurred in the course of once popular serum therapy and were attributable to sensitization to horse serum.

Death from skin testing has been previously reported, as far as we have been able to determine, only 10 times. In only 3 cases were autopsies performed. In 1922 Cooke[6] reported the death of a 3 year old asthmatic child, occurring in 3 minutes after an intracutaneous test with 0.01 cc. of LePage Glue (0.1 mg. N/cc.). The symptoms were urticaria, edema, cough, dyspnea and cyanosis. In 1924 Lamson[16] reported the death in 2½ hours of a child with eczema after the injection intracutaneously of 0.05 cc. of egg white (0.15 mg. N/cc.) Cyanosis and edema characterized the episode. In 1928 Baagoe[3] reported death after sudden collapse in dyspnea of a patient who had received a test dose of 0.1 cc. of egg white. In 1929 Lamson[17] again reported the death of an asthmatic man, 34 years old, occurring 5 minutes after an intracutaneous test dose of 0.02 cc. of 1-500 buckwheat solution. The symptoms were cyanosis and dyspnea. In 1935 Freedman[10] reported the death of an asthmatic child 6 years of age, in 8 minutes after receiving 0.05 cc. of horse serum intracutaneously. The symptoms were urticaria, cyanosis and abdominal pain. In 1940 Ferguson[9] had a similar experience when 0.18 cc. of antitetanus serum was injected as a test intracutaneously into a 6 year old boy. Bloody mucous expectoration, dyspnea and urticaria preceded death 2 hours later. In 1942 Vance and Strassmann[26] reported the death of a 4 year old asthmatic girl with cyanosis, shock and coma occurring 3 minutes after skin testing with silk, wool and kapok. In 1943 Hunt[14] tested a 22 year old asthmatic woman with 0.2 cc. of guinea pig hemoglobin in saline. Death occurred in 10 min-

utes. Cyanosis and dyspnea were the symptoms. Wiseman and McCarthy-Brough[32] reported in 1945 the case of a 78 year old woman with life-long asthma who developed cough, dyspnea, cyanosis and coma and succumbed in 15 minutes after 17 intradermal tests in doses not greater than 0.02 cc. Six years before this she had been tested with similar extracts without untoward effects. Swineford in 1946[21] reported a case of a 49 year old woman with asthma who died 15 minutes after the onset of apprehension, cyanosis and dyspnea in the course of multiple skin testing. The offending antigen was not discovered.

Case Report. Mrs. Z. V. M., a white woman, aged 57, was referred for allergic study on account of asthma which she had had perennially with fall exacerbations since onset in 1914. At that time she was living in a damp mining town. In Mexico, where she next lived from 1924 to 1938 at an altitude of 6,500 feet, she had very few symptoms. She was especially free in the dry season. In 1938 she moved to Texas where her symptoms returned and were considerably worse. For the last 3 months (October, November, December, 1946) she had lived in Richmond, Virginia, where her attacks had become increasingly severe. She had been twice skin tested; the last time in June, 1945, in Nashville, Tennessee, where she gave strong reactions to cat hair, chicken and duck feathers, house dust and Bermuda grass. A number of other tests were said to have been negative. In 1933 the basal metabolic rate was said to have been minus 9. In 1943 and again in 1946 electrocardiographic tracings were reported as normal. Her father had had hay fever and migraine; a paternal grandfather, hay fever, asthma and migraine. As a child she herself had had frequent head colds and attacks of urticaria. She later developed symptoms suggestive of migraine. She reported that her attacks of asthma responded well to pyribenzamine orally and to aminophyllin intravenously, but she was violently opposed to the use of adrenalin, stating that it had produced immediate and alarming symptoms whenever given.

Physical examination revealed a well-nourished gray-haired woman, 5 feet 4 inches tall, weighing 136 pounds, with a temperature of 98° F., pulse 82, and blood pressure 170/118. She was in no distress. The heart appeared normal, and aside from congestion of the nasal mucous membrane and diffuse wheezes throughout both lung fields, nothing of significance was made out. The urine was normal. Her hemoglobin was 16.3 gm., red blood cell count 4,930,000, and white blood cell count 8,400, with 67% polymorphonuclear leukocytes and 12% eosinophils. The sedimentation rate was 14 mm. in 60 minutes. Nasal blowings contained 5% eosinophils.

Preliminary scratch tests on the arms to groups of trees, grasses, weeds and flowers and to cottonseed, flaxseed, condiments, fish, mollusks, and egg were all negative. Intracutaneous tests, using the back, were then begun to the common foods, to cat, dog and cattle hair, and to chicken and duck feathers.* Fifty-six skin tests had been completed without any positive reactions, when she suddenly complained of air hunger and sat up to get her breath. Seen immediately by a physician, her expression was anxious, and she was moderately cyanosed. She was obviously having great difficulty getting her breath. Wheezing respiration was heard over the whole chest and the heart sounds were plainly audible. She was given 0.5 cc. of epinephrine intramuscularly without effect, followed by a hypodermic of 1/6 grain of morphine. She died 15 minutes after the onset of symptoms. In the excitement incident to this unexpected reaction, no attempt was made to read the skin tests finally, but the impression was that none of them had been positive.

An autopsy, performed 2 hours after death, was limited to the thorax and to the examination of the liver. Both chest cavities were filled by strikingly voluminous lungs. The left lung was bound to the thoracic wall by cobweb adhesions. The right lung was firmly adherent to the posterior wall of the thorax and to the dome of the diaphragm. When removed, both lungs failed to collapse, floated high in water, were pale, and markedly emphysematous. There were no large blebs on their surfaces. There were numerous small subpleural hemorrhages over the right lower lobe. There were submucous hemorrhages in the trachea which was pale and free of swelling or secretion. The same appearance was observed in the primary and secondary bronchi. No mucous plugs were seen. The heart was normal and contracted. All the cavities except the right auricle were devoid of blood. Sections of the lung showed hyaline thickening of the basement mem-

*All extracts were made by an experienced technician by the method described by Vaughan[27] (p. 272).

brane, round cell and eosinophilic leukocytic infiltration and edema of the walls of the secondary bronchi. The infolding of the mucous membrane of the bronchi was striking and strongly suggestive of spasm as an occluding factor. Marked mucin-secreting activity of the cells of the mucous membrane of the bronchi as well as of the mucous glands was observed. The lumens of the bronchi were partly filled with mucin. Less marked changes were observed in the smaller bronchi. Emphysema was striking. The trachea showed edema. The myocardium was normal.

Discussion. The course of events in this case raises several controversial questions. The first involves the relative advantage and risk of multiple, one-sitting skin tests as against what is perhaps commoner, the method of serial testing with a limited number of allergens at a time. Pratt in 1938,[18] from guinea pig experiments, concluded that "when either of 2 antigens alone is capable of producing moderate anaphylactic shock in specifically sensitized guinea pigs, the sum of these antigens in a single dose does not enhance the degree of shock, whereas doubling the shocking dose of either antigen alone results in an increased response." Waldbott[30] at the same time observed: "200 or 300 skin tests are often given at one sitting and only rarely do constitutional reactions occur, in spite of the fact that many skin tests may be positive. If there was an accumulative effect of antigens, we would encounter constitutional reactions on skin testing much more frequently." Swineford in 1941[22] quoted the above and condensed his findings in the conclusion that: "no evidence has been found in the literature to support the statements that routine multiple skin testing is more dangerous than a few tests at one sitting."

On the other hand it has long been a clinical dictum that sensitive individuals exposed to one antigen are much more apt to exhibit symptoms if subjected simultaneously to another antigen to which they are also sensitive. Thus a ragweed-cat-sensitive child may be free of symptoms in August if the cat is sent away, and may play with the cat with impunity during other months of the year. But to play with the cat in August is a sure way of precipitating an asthmatic attack. In 1922 Cooke,[6] although unable to prove it, thought that a reaction to multiple skin testing was "more likely to ensue as a result of the sum total effect of all the allergens exerting their influence upon the same reacting mechanism." It is not unusual during skin testing for a single massive reaction to herald a severe constitutional reaction. But this is not always the case. A reaction so severe as to cause death in a few minutes, as in the case reported, may give no warning in the degree of reactivity. Gay[11] has observed that "skin reactions and constitutional behavior do not necessarily parallel one another."

Can epinephrine, a drug so feared by the patient on account of previous distressing symptoms, have had anything to do with the results? Deissler[27] has described a case sensitized to epinephrine. Occasionally hypersensitivity followed by major accidents has resulted from the use of epinephrine. Sudden death has resulted from the injection of 1 cc. of a 1-1,000 solution.[8]

Can the employment of morphine in this case have contributed to the end result? There is opposition among allergists as a group to the use of morphine in the treatment of asthma. A drug which depresses the respiratory center and stimulates bronchial spasm, however slight, has been regarded as a possible determining factor in many cases of fatal asthma. But reference to the literature of allergy on the use of morphine in asthma leaves the average physician in somewhat of a quandary. One group of authors unequivocally

condemns it.[4,12,23,25,28] Another recommends its use with reservations.[1,19,24] While still a third group supports its use, Coke[5] advising that "The next step to take in cases in which adrenalin is without effect is to give an injection of morphine. I think it is important to give enough morphine." In Walzer's opinion "morphine is a valuable drug for controlling a severe asthmatic paroxysm."[31] Cooke summarily dismisses the question stating that "There are many who believe that opium and its derivatives should never be used in asthma. I do not concur."[7] The employment of morphine in our case was a mistake. Our own opinion is emphatically against its use in the treatment of asthma of any type.

The employment of the back in preference to the arms as a test site raises also the question of relative risk. In case of a constitutional reaction, a tourniquet can be applied to the extremity, if the arm has been used, and should reduce or delay the absorption into the general circulation of a toxic substance injected into the skin distal to the point of application. On the other hand, it is our belief that by the time a tourniquet can be applied, an irreversible train of circumstances has often been set in motion. After all, our chief reliance in cases of constitutional reaction is in epinephrine. The back is favored because of convenience. It offers a large area for testing so that test sites need not be crowded. Injections are less painful and the skin of this region as shown by Alexander and McConnell[2] is more reactive than the arm. This does not imply that constitutional reactions are more apt to arise from such injection sites. There are too many factors to be taken into consideration to speak dogmatically. When the arms are used for preliminary scratch tests, we believe that the employment of the back for intracutaneous testing is reasonably safe. By this method we have performed thousands of skin tests with very few systemic reactions.

What was the mechanism of death in this case? It is not enough to say that the patient died of asphyxia resulting from bronchial obstruction. The usual answer is that edema of the walls of the small bronchi, plus smooth muscle spasm, plus mucous plugging of the lumens of the bronchi in varying combinations produces the obstruction. Edema is so fundamental to human allergy, and can develop so rapidly as in cases of generalized urticaria, that this factor, plus the mucous plugs which are easy to demonstrate after death, is usually regarded as a primary cause of fatal bronchial obstruction. On the other hand, bronchial spasm is easily demonstrated as the essential factor in death in guinea pig anaphylaxis. Huber and Koessler[13] made numerous micro measurements and appear to have shown hypertrophy of bronchial smooth muscle in asthmatic subjects. Klemperer[15] reminds us that hyperactivity of smooth muscle is also fundamental to the allergic reaction and need not be associated with any obvious morphological lesion, maintaining that "the gross anatomy of bronchial asthma shows only the result of the spasm of the small bronchioles." In the case reported here, as one viewed the lungs in the gross and studied the sections under the microscope, direct evidence of spasm or of extensive edema was lacking, unless one is willing to accept the infolding of the mucous membrane as indicating smooth muscle contraction of the bronchial walls. Mucus in the lumens of the small bronchi was impressive, but aside from this the cause of obstruction remained a matter of conjecture.

Summary. A case of death with autopsy is reported occurring in the course of routine skin tests in a woman

who had been safely skin tested on 2 previous occasions. Death was without the warning of at least one massive skin reaction and occurred 15 minutes after the onset of symptoms. Neither edema nor urticaria was manifest and death was thought to be the result of asphyxia from bronchial obstruction. The effect of multiple intracutaneous skin tests applied to the back and the possible influence of epinephrine sensitivity and of morphine have been considered.

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STUDIES IN THE RELATION OF THE HEMOLYTIC STREPTOCOCCUS TO RHEUMATIC FEVER

INFECTION, AND OTHERS*†

V. STREPTOCOCCAL ANTI-HYALURONIDASE (MUCIN-CLOT-PREVENTION) TITERS IN THE SERA OF PATIENTS WITH RHEUMATIC FEVER, STREPTOCOCCAL

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THE etiology of rheumatic fever is at present unknown. Of the recorded clinical and experimental studies of this disease 2 categories of observations, the epidemiologic[15] and immunologic,[5] have yielded suggestive evidence of a possible specific etiologic agent, in both cases the hemolytic streptococcus. However, extensive investigations of the relation between this organism and rheumatic fever have failed to point to any constituent or product of the streptococcus which might be the immediate cause of the phenomena of rheumatic fever, or to any mechanism by which such an agent could exert its effects.

As part of a systematic investigation in these laboratories[6,7] of the relation between the hemolytic streptococcus and rheumatic fever, a biologic property of the hemolytic streptococcus which must be considered is the production of hyaluronidase. This aspect of the investigation has especial current interest because the possible role of streptococcal hyaluronidase in the pathogenesis of rheumatic fever has been the subject of some recent speculation.[14] The basis for this speculation lies in the facts that rheumatic fever is a disease of hyaline connective tissue, that hyaluronic acid, which characterizes hyalin, is depolymerized by hyaluronidase,[12] and that the hemolytic streptococcus is one of the bacterial species which produces this enzyme.[13]

The effect of streptococcal hyaluronidase as a spreading factor in the tissues of rheumatic subjects has been studied elsewhere.[8] In this investigation antibodies to this enzyme have been measured in such patients. Of the methods available for measuring this enzyme *in vitro* the mucin-clot-prevention (M.C.P.) test[17] was used. This test is one of three available physico-chemical tests for the activity of hyaluronidase the others being the turbidimetric and viscosimetric, respectively. The reason for the choice of the M. C. P. test and the possible differences among the tests are presented elsewhere.[3] This method has been used for measuring antibodies to clostridial[11] and streptococcal hyaluronidase. In the latter case, Friou and Wenner[2] have shown that many normal human sera contain neutralizing substances for streptococcal hyaluronidase. Using an index which compares the amount of enzyme neutralized by constant amounts of experimental sera, these

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authors found that of 21 rheumatic patients, 20 showed indices of neutralization higher than was normal for that age-group. These inhibition ratios were not strikingly different from those found in convalescents from streptococcal infections.

Methods and Materials. *Hyaluronic Acid.* In various stages of the preparation and use of this reagent it may be in the form of hyaluronic acid or of potassium hyaluronate, but for simplification of nomenclature we shall make all references to it as hyaluronic acid. The method used for preparing this substrate was adapted from that of McClean, *et al.*[11] Three modifications of the method they described were found to be advantageous: (1) The suspension of minced umbilical cord was treated in the Waring blendor at each extraction, with a resultant marked increase in yield of hyaluronic acid; (2) the solution of crude hyaluronate was poured into the alcohol-potassium acetate solution, rather than vice versa. In addition to a better precipitation of the hyaluronic acid an important advantage of this modification is the fact that 95% ethyl alcohol may be substituted for absolute alcohol under these circumstances; (3) the clot of hyaluronic acid was minced with scissors and allowed to dry in air, in a shallow horizontal layer from which the ether was removed by suction.

The hyaluronic acid, as prepared in this way, was white or tan in color and could be redissolved with ease for testing. The average yield was approximately 0.9% of the weight of umbilical cords as stored in acetone.

Hyaluronidase. Streptococcal hyaluronidase was prepared from a suitable strain of group A hemolytic streptococcus, H_{44}, which was supplied through the courtesy of Dr. Karl Meyer. It was found that the culture supernate afforded an abundant and simple source of the enzyme, so that this was used as starting material, rather than extracts of whole streptococci. The hyaluronidase-containing material was prepared as follows: Three liters of dextrose broth (Difco) or of a protein-free medium described elsewhere,[10] were seeded with 300 cc. of a 6 hour seed culture. After 18 hours of incubation the culture medium in which the streptococci had grown was freed of the organism by centrifugation and concentrated approximately 10 fold by pervaporation overnight. The concentrated medium was then freed of residual streptococci by centrifugation at 5000 R.P.M. for 30 minutes and dialyzed overnight against running tap water. After final dialysis against distilled water the preparation was desiccated from the frozen state and stored at -10° C., not *in vacuo*. It was found that the potency of the preparation remained unchanged for many months.

Pneumococcal and clostridial hyaluronidase were prepared in a similar way. In the latter case thioglycollate medium was used rather than dextrose broth. Testicular hyaluronidase was prepared according to the method of Madinaveitia.[10]

Hyaluronidase and Anti-hyaluronidase Tests. These tests were performed, with minor modifications, according to the technic of McClean, *et al.*[11] The relative volumes of the reagents in the anti-hyaluronidase test were suggested by technical factors, and by the desirability of making the serum dilutions generally similar to those used in other serologic tests of the same sera in progress at the time. The volumes of reagents in the hyaluronidase tests were in turn adjusted to reach the same total volume as the reagents in the anti-hyaluronidase test, since the former was essentially used in calibrating the neutralization test.

In the hyaluronidase test, 0.2 cc. of a solution of the hyaluronidase preparation dissolved in physiologic saline solution was incubated with an equal volume of a solution of potassium hyaluronate. The latter contained 2 mg. of hyaluronic acid per cc. in distilled water, with one-sixteenth volume of normal horse serum added. An additional 0.4 cc. of physiologic saline solution was present in each tube. As soon as the enzyme had been added to the substrate, the tubes were incubated at 37° C. for 20 minutes. At the end of that period the tubes were quickly transferred to an ice-water bath. After 5 minutes of chilling, 0.2 cc. of 2 N acetic acid was added to each tube. The

racks were shaken vigorously and the clots were read. The appearance of a flocculent precipitate was taken as evidence of essentially complete digestion of the hyaluronic acid, a small but single fibrous clot was taken as evidence of partial digestion, and a mucin clot fully as large as that in control tubes without hyaluronidase was considered negative for hyaluronidase activity.

In the anti-hyaluronidase test the enzyme was used in 3 times the amount which caused partial digestion of the hyaluronate, or twice the amount which caused almost complete digestion. The use of a smaller number of units of enzyme in the neutralization tests was found to cause ragged clots and poorly defined endpoints. The successive 2 fold dilutions of serum, in volume of 0.4 cc. were incubated for 20 minutes at room temperature with 0.2 cc. of the solution of hyaluronidase. The concentration of the latter had been adjusted, on the basis of preliminary hyaluronidase tests, so that 0.2 cc. contained 3 units as defined above. The hyaluronate-horse serum solution was now added as in the case of the hyaluronidase test described, and the test was completed in the same way. The initial dilution of serum corresponding to the last tube which showed a full clot was considered the titer of the serum. If this tube was succeeded by one in which there was a smaller mucin clot, rather than a flocculent precipitate, indicating partial neutralization, the titer was considered to be half a 2 fold step higher.

The Preparation of Sera. The sera of newborn infants were prepared from blood collected from the umbilical cords in the delivery rooms of the Philadelphia General Hospital. The sera of older infants were collected in the wards and outpatient department of The Children's Hospital of Philadelphia. These infants ranged in age from 6 months to 3 years. The sera representing the antibody levels in normal children were collected at The Children's Hospital of Philadelphia, and in local private schools. The sera of young adults were collected at the Student Health Service of the University of Pennsylvania, and in the Maternity Wards of the Philadelphia General Hospital.

For the study of the anti-hyaluronidase titer in acute streptococcal disease, blood specimens were collected from children with scarlet fever at the Philadelphia Hospital for Contagious Diseases, during the first half-week and during the third week of the disease. These patients were not treated with sulfonamides. In a number of these cases, additional specimens were drawn 3 weeks or 4 months later.

In the case of rheumatic patients the blood specimens were drawn at weekly, bi-weekly, or monthly intervals, depending on the severity of the rheumatic process, in correlation with the clinical studies to be described below.

Blood specimens were collected with a minimum of sodium citrate as anticoagulant, in order to allow for the determination of the erythrocyte sedimentation rate, white blood count, and concentration of hemoglobin. The plasma was drawn off each blood specimen and frozen as soon as the tests above had been completed. When a specimen was to be tested, it was thawed, cleared by centrifugation of the fibrinogen which had precipitated on freezing, and diluted for the test. A single dilution of 1:8 or 1:16 was made of each serum, in comparative estimations of anti-hyaluronidase and antibodies to other streptococcal antigens.

The Study of the Patients and the Criteria of Activity of the Rheumatic Process. The rheumatic patients were studied in acute, convalescent and quiescent stages of the disease in the institutions from which this work is reported. The patients were examined at least every 2 weeks while in the acute or convalescent wards and at each visit to the clinics. These examinations included the following: *symptoms*—anorexia, headache, precordial, abdominal or arthritic pain, cough, dyspnea, and epistaxis; *physical signs*—cardiac rate and rhythm, distance of apex beat from the midline, murmurs, with distance of transmission of each, and other adventitious sounds, palpable thrills and friction rubs, hepatic enlargement and edema, rashes, subcutaneous nodules and chorea. Laboratory examinations included the erythrocyte sedimentation rate, white blood cell count and hemoglobin concentration. The vital capacity was usually

determined at bi-weekly intervals, and electrocardiograms were taken as required. The erythrocyte sedimentation rate was done by a method described elsewhere.[4] It involved a series of readings of the erythrocyte level at 5-minute intervals, in order to determine the rate of free fall of the corpuscles, and a correction for the relative volume of erythrocytes.

The patients selected for serologic study were, of course, only those in whom the diagnosis of active rheumatic fever was beyond doubt. All the children who are referred to in this paper as active rheumatics had active carditis.

The amount of hyaluronic acid was now kept constant at a level (0.4 mg. in 0.2 cc.) which would give an easily discernible and substantial clot (half that amount barely sufficed to produce a small mucin clot) and the concentrations of enzyme and serum were varied simultaneously, in order to ascertain the relationship between these two reagents. The results of such an experiment, as seen in Table 2, show that an inverse proportion exists between the amount of enzyme used, and the dilution of serum which suffices

TABLE 1. QUANTITATIVE RELATIONS BETWEEN HYALURONIDASE AND HYALURONIC ACID

Hyaluronidase	*Hyaluronic Acid, mg.*				
mg./cc.	0.8	0.6	0.4	0.3	0.2
0.18	1	0	0	0	0
0.13	1	0	0	0	0
0.09	2	1	0	0	0
0.06	2	2	±	0	0
0.04	2	2	1	0	0
0.03	2	2	2	±	0
0.02	2	2	2	1	±
0	2	2	2	2	±

2 = full mucin clot (of native hyaluronic acid)
1 = smaller clot
± = shreds of clot
0 = amorphous precipitate (of depolymerized hyaluronic acid)

Results. *Quantitative Relations among Substrate, Enzyme, and Neutralizing Antibody.* Preliminary experiments were carried out on the quantitative relations of the reagents. The relation between concentrations of hyaluronidase and hyaluronic acid was investigated by allowing various quantities of the enzyme to act on different amounts of the substrate. The results of a typical experiment of this sort are shown in Table 1.

The data in Table 1 show essentially a direct proportion between the amount of hyaluronic acid present in the tube and the amount of hyaluronidase required to digest it over the narrow range in which this test was practicable. Similar results were obtained by McClean[11] in the case of testicular hyaluronidase.

to neutralize it. The end points thus fall in a straight line, inclined at 45°, which is characteristic of *in vitro* immunologic neutralizations. In the rows which represent the smallest amounts of the enzyme, it is seen that the end point of neutralization is indistinct. For this reason the amount of hyaluronidase used in the mass serologic tests was that corresponding to row C in this experiment.

Reliability of Measurements of Hyaluronidase by the Mucin-Clot Prevention Test, by Comparison with Spreading Potency in the Skin. It was mentioned above that of the 3 available *in vitro* tests for hyaluronidase the M.C.P. test was chosen because it was more suitable for adaptation to this study. It was therefore thought advisable to confirm the reliability of this

test. An opportunity to compare the M.C.P. test, as done in the work here reported, with the spreading test was afforded by work done on purification and sterilization of streptococcal hyaluronidase reported elsewhere.[8] Preparations of hyaluronidase which had been examined for spreading potency in the rabbit's skin were titrated for hyaluronidase by the M.C.P. test. Results of such tests are given in Table 3. The Table shows that the M. C. P. titration of hyaluronidase preparations agrees well with the titration of the same material by actual spreading effect in the skin.

Table 2. Quantitative Relations between Streptococcal Hyaluronidase and Its Neutralizing Antibody

	Hyaluronidase	*Dilution of Serum 5507*								
		1:64	1:128	1:256	1:512	1:1024	1:2048	1:4096	1:8192	—
	mg./cc.									
A	0.5	♀	♀	0	0	0	0	0	0	0
B	0.25	♀	♀	1	0	0	0	0	0	0
C	0.125	♀	♀	♀	1	0	0	0	0	0
D	0.063	♀	♀	♀	♀	1	±	0	0	0
E	0.031	♀	♀	♀	♀	♀	1	1	±	0
F	0.016	♀	♀	♀	♀	♀	♀	♀	♀	0

♀ = full mucin clot (of native hyaluronic acid)
1 = smaller clot
± = shreds of clot
0 = amorphous precipitate (of depolymerized hyaluronic acid)

The Serologic Specificity of the Neutralizing Antibodies to Streptococcal Hyaluronidase in Sera of Human Subjects. In initial exploratory work a miscellaneous group of sera from apparently normal subjects was tested for the presence and concentration of neutralizing substances for streptococcal hyaluronidase (anti-hyaluronidase). It was found that measurable amounts of such neutralizing substances were present in almost every serum tested, in titers varying over a wide range. The same observation has since then been reported by others,[2] as noted above.

These data did not indicate whether we were observing the effect of a specific neutralizing antibody or of some constituent of serum which might interfere with the biochemical action of hyaluronidase or hyaluronic acid. In order to test the specificity of the reaction, parallel anti-hyaluronidase tests were done versus testicular, pneumococcal and clostridial hyaluronidase. Each of the other enzymes was, of course, present in the same number of units of potency as the streptococcal hyaluronidase.

Table 4 gives the results of such tests. These data show that the human sera tested did not interfere with the digestion of hyaluronic acid by clostridial or testicular hyaluronidase. Some of these sera did neutralize pneumococcal hyaluronidase, but in a much lower range of titers than in the case of the streptococcal enzyme. There was, moreover, no correlation between anti-pneumococcal and anti-streptococcal titers.

Recent studies in collaboration with Dr. Dan H. Moore indicate that the neutralizing antibody to streptococcal hyaluronidase is in the gamma globulin fraction of electrophoretically separated serum.

The Titer of Antibodies to Streptococcal Hyaluronidase in Normal Individuals of Various Age-Groups. As a preliminary to the study of these antibodies in streptococcal and rheumatic infection it was necessary to study the titers found in the presumably normal population. These determinations included those on sera of 94

neonatal infants, 118 older infants (6 months to 3 years of age), 185 children (4 years to 15 years of age) and 135 young adults.

The results of these determinations are shown in a percentage-frequency chart in Fig. 1. It can be seen in the Figure that antibodies to streptococcal hyaluronidase were found among all age-groups. Among the infants most sera were found to contain no measurable amount of neutralizing antibody to streptococcal hyaluronidase. reflected completely the pattern of their mothers, who were included among the young adults.

Antibodies to Streptococcal Hyaluronidase in Scarlet Fever. In order to observe the effect of acute infection by the hemolytic streptococcus on the titer of this antibody, sera were obtained from children with acute scarlet fever (within the first 5 days after the onset of symptoms) and at the end of the 3rd week of the disease. Of the 130 such pairs of sera collected, 34

TABLE 3. COMPARISON OF THE MUCIN-CLOT-PREVENTION TEST FOR HYALURONIDASE WITH SPREADING POTENCY

Material	*Assay of Hyaluronidase In Vivo and In Vitro*							
	Spreading potency, Minimal effective dose	*Results of M.C.P. Test* *Mg./cc. of enzyme preparation*						
		0.25	0.125	.06	.03	.015	.008	.004
	mg.							
CS 119 Original	.006	0	0	0	±	1	2	2
CS 119 partially purified	.003	0	0	0	0	0	1	2
CS 119 partially purified, irradiated	.006	0	0	0	0	1	2	2
CS 119 partially purified, glass-filtered	.012	0	0	0	1	2	2	2
CS 119 partially purified, Seitz-filtered	.048	0	1	2	2	2	2	2

2 = full mucin clot (of native hyaluronic acid)
1 = smaller clot
± = shreds of clot
0 = amorphous precipitate (of depolymerized hyaluronic acid)

The antibody titers of the remaining infants were low and the majority fell in the range between 8 and 16. The sera of children of slightly older age showed more antibody to streptococcal hyaluronidase. There were fewer sera with no measurable antibody. The range of titers was distinctly wider, the greatest aggregation of titers appearing between 8 and 128. The sera of young adults were grouped about a mean titer of 32, with 65% falling between 16 and 64. Neonatal infants were followed by a third specimen which was obtained either 3 weeks or 4 months after recovery from the acute illness. The percentage-frequency charts of titers found in the same children at the onset of scarlet fever and 3 weeks thereafter are shown in Fig. 2. These charts show that the titers are generally higher as a result of the streptococcal infection. The mean anti-hyaluronidase titer found during the 3rd week of the disease was 73, in comparison with the geometric mean titer*

* The geometric mean titer is obtained by noting the logarithms of the individual titers to the base 2 (since the dilutions are made in 2-fold steps). The average of these logarithms is then computed, and the antilogarithm of this average is the geometric mean. This procedure is necessary because the conventional dilutions of sera in such tests result in a geometric series of decreasing concentrations, and because of the characteristic distribution of antibody titers in human groups.

of 20 which had been found at the onset of the disease. Of the individual pairs tested, 45% showed no significant increase in titer, 22% a 2-fold rise, and 33% a 4-fold or greater rise.

Anti-hyaluronidase titers were observed 6 weeks after the onset of the acute episode of scarlet fever in 15 children. When these were compared with those of the same children during the 3rd week of the disease it was found that in somewhat more than half, the titer had not changed significantly from the time of clinical convalescence to 3 weeks thereafter. Most of the others showed a slight increase in titer. The mean titer of this group was 120.

Of the patients whose serum specimens were obtained 4 months after acute scarlet fever 88% showed anti-hyaluronidase titers which were at least as high as at the height of the disease.

Anti-Hyaluronidase Titers in Acute and Quiescent Rheumatic Fever. Neutralizing antibodies to streptococcal hyaluronidase were measured in the sera of 135 patients with quiescent rheumatic disease. The range of titers found, from less than 8 to 256, was similar to that found in the normal children of comparable age, and the geometric mean titer was 52.

Among 160 children with active rheumatic carditis the anti-hyaluronidase titers were found to be much higher. The range of titers, except for 3 values of 32, was from 128 to 4096, with a geometric mean titer of 580. These distributions are shown in Fig. 2. This Figure shows also that the anti-hyaluronidase titers in acute rheumatic fever were higher than those following scarlet fever.

TABLE 4. SPECIFICITY OF NEUTRALIZING ANTIBODIES TO STREPTOCOCCAL HYALURONIDASE

	Titer of Neutralization of Hyaluronidase			
Source of Serum	*Streptococcal*	*Pneumococcal*	*Clostridial*	*Testicular*
Normal child	32	—	—	—
Normal child	64	—	—	—
Normal child	8	12	—	—
Normal child	48	6	—	—
Normal child	128	—	—	—
Normal youth	48	—	—	—
Normal youth	24	8	—	—
Normal youth	32	—	—	—
Normal youth	96	—	—	—
Quiescent rheumatic	64	—	—	—
Quiescent rheumatic	192	—	—	—
Quiescent rheumatic	96	—	—	—
Quiescent rheumatic	96	6	—	—
Convalescent from scarlet fever	384	—	—	—
Convalescent from scarlet fever	768	—	—	—
Convalescent from scarlet fever	512	8	—	—
Convalescent from scarlet fever	256	12	—	—
Acute rheumatic	1024	—	—	—
Acute rheumatic	768	—	—	—
Acute rheumatic	2048	—	—	—
Acute rheumatic	512	—	—	—
Acute rheumatic	512	6	—	—
Acute rheumatic	2048	—	—	—
Acute rheumatic	1024	6	—	—

— = less than 4

Anti - Streptococcal - Hyaluronidase

Titers during Fluctuations in the Severity of the Rheumatic Process. Almost all the patients in the acute rheumatic group were followed for considerable periods of time. Among patients who showed continued activity of the rheumatic process of constant or fulminating severity, the anti-hyaluronidase titer remained elevated. The majority of patients studied were observed during a single episode of the disease, with a decline in the acuity of the illness to quiescence. In these patients it was found that the anti-hyaluronidase titer did not decline with the clinical severity of the disease, but remained in the same range for a considerable period of time after the rheumatic infection had become quiescent. The fall in concentration of these antibodies was noted in many of these patients some months thereafter.

Finally, some of the patients showed a polycyclic course, so that it was possible to observe the correlation in a given patient between the clinical activity of the rheumatic disease and the serum titer of anti-hyaluronidase.

In the case of patients whose rheumatic process had been quiescent for

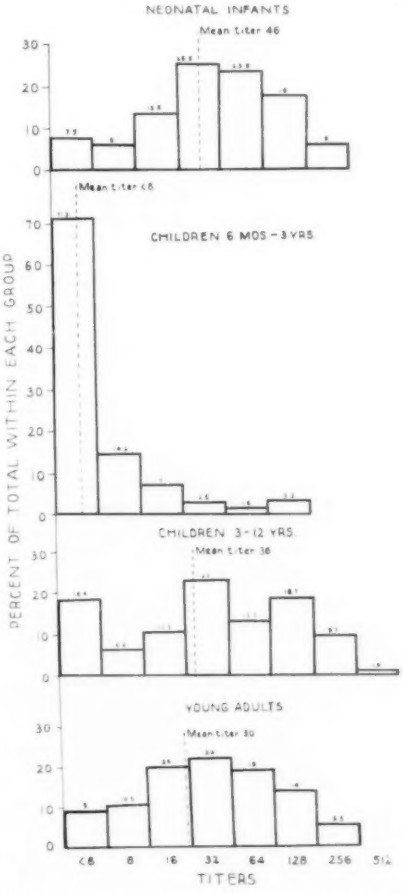

Fig. 1.—The frequency distribution, in percentage, of streptococcal anti-hyaluronidase titers in normal subjects of various age-groups. The percentages are given by the small numbers at the head of each column.

some time, so that the anti-hyaluronidase titer had declined from the original elevated value, the titer of this antibody rose again at the time of the rheumatic recrudescence. Smaller fluctuations of the activity of the rheumatic process, or rheumatic recrudescences not separated by considerable intervals of time, however, were not accompanied by definite changes in anti-hyaluronidase titer. Clinical details of the study of variations in rheumatic activity in correlation with the anti-hyaluronidase titer will be presented elsewhere.[9]

Discussion. *The Mucin-Clot Prevention Test as an In Vitro Measure of Hyaluronidase.* As was stated above, the choice of the M.C.P. test for this work was made on the basis of adaptability to serologic analysis. Because of this, and because the precise chemical basis of the mucin clot reaction is not understood, it was advisable to test the reliability of this reaction. In all work on the measurement of hyaluronidase *in vitro*, the spreading potency in the skin has been used as the standard of comparison, since the latter affords a direct observation of the biologic phenomenon involved. The titration of spreading factor cannot be made in steps smaller than 2-fold, and within

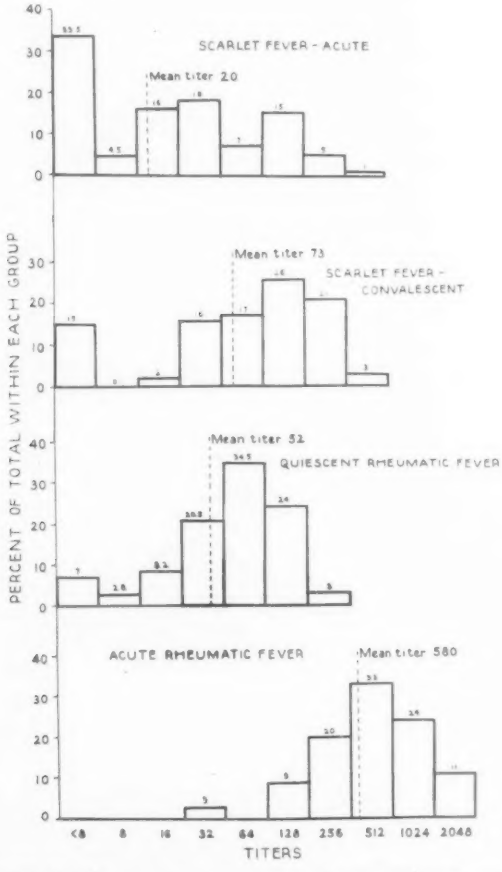

Fig. 2.—The frequency distribution, in percentage, of streptococcal anti-hyaluronidase titer in streptococcal infection and rheumatic fever.

this limitation excellent agreement was found in this study between spreading potency and the M.C.P. measure of hyaluronidase in various preparations incidental to purification and sterilization of the enzyme.

The Occurrence of Neutralizing Antibodies for Streptococcal Hyaluronidase in the Normal Population. This finding is of interest with regard to the production of hyaluronidase by hemolytic streptococci and with regard to the epidemiology of this organism.

Freshly isolated strains of group A hemolytic streptococci have been examined by several authors for production of hyaluronidase *in vitro*. Of several strains tested, detectable amounts of this enzyme were found only in strains of type 4 by Hobby, *et al.*[9] Crowley[1] found that only one additional type, type 22, of a total of 308 isolations of hemolytic streptococci, produced demonstrable hyaluronidase in culture. The finding of neutralizing antibodies to streptococcal hyaluronidase in almost all the tested sera derived from the presumably normal population past infancy must mean, however, as Friou and Wenner[2] have pointed out, that the enzyme is in fact produced by all or almost all strains of group A hemolytic streptococci, but often in such small quantities as to be detectable only indirectly, by means of the relatively large amounts of antibody to which minute amounts of the enzyme give rise. The circumstance which makes possible such detection is the broad reactivity of streptococcal hyaluronidase within group A.

The other implication of the widespread occurrence of anti-streptococcal-hyaluronidase in normal sera is also of epidemiologic interest, since this wide occurrence of the antibodies points to the ubiquitous character of the hemolytic streptococcus as an invader of the human upper respiratory tract, whether or not acute infection is present.

It is of some interest to compare the antibody titers to streptococcal and pneumococcal hyaluronidase. The latter antibody is met with such frequency that there can be little doubt that, as in the case of group A hemolytic streptococci, the enzyme is broadly reactive and is produced by the great majority of strains. The striking difference in range of neutralizing titers against enzymes of these two sources implies that although both streptococci and pneumococci are found in the normal and inflamed human throat, the streptococcus must be much more prevalent and effective as an invader of the human host.

The fact that no neutralizing effect could be found to testicular or clostridial hyaluronidase indicates that the anti-hyaluronidase effects measured involved true neutralization by antibodies, rather than non-specific interference by some constituent of serum with the enzymatic activity of hyaluronidase.

The occurrence of antibodies to streptococcal hyaluronidase in the population at large, and the rising range of titers with increasing age is, then, explained on the basis of 2 facts: broad reactivity of streptococcal hyaluronidase within the group of human pathogens, and the prevalence of contact between the streptococcus and the human host. A similar explanation was given for the widespread occurrence of of complement-fixing antibodies to somatic fractions of the hemolytic streptococcus, described elsewhere.[6]

The range of titers in the normal children, and in acute streptococcal infection, is less uniform in the case of anti-hyaluronidase than in the case of antibodies to those fractions. This may well be due to the fact that the percentage content of each somatic fraction probably varies only slightly among strains of hemolytic streptococci, whereas the rate of production of the

enzyme may well vary over a range of several orders of magnitude. Thus the antigenic stimulus of the latter case may vary quite widely, with corresponding variations in the resulting titer of antibody. The same consideration would apply to the "booster" effect of subclinical contacts with the hemolytic streptococcus, which is responsible for the sustained elevation of anti-hyaluronidase titers after acute streptococcal or rheumatic infection.

The Significance of Elevated Anti-Hyaluronidase Titers in Acute Rheumatic Fever. The data presented here show unequivocally that the streptococcal anti-hyaluronidase titer is elevated in acute rheumatic fever. On comparing the titers found in acute and quiescent rheumatic fever, it was found that 84% of the values found in the acute group were 384 or more, and thus were higher than any found among the quiescent rheumatics. The geometric mean titers were 580 and 52, respectively. The anti-hyaluronidase level referred to, 384, was also higher than 98% of the presumably normal controls, whose geometric mean titer was 36. The data given certainly point to an extensive contact with the hemolytic streptococcus in the recent history of a patient with acute rheumatic fever, which is in agreement with almost all of the serologic work which has been done on this problem.

The comparison of the anti-hyaluronidase titers of acute rheumatic subjects with those of a group of convalescents from a frank streptococcal infection, scarlet fever, is, however, of some interest, for it is seen that the mean titer in active rheumatic fever is 8 times as high as it is following scarlet fever, with corresponding differences in the distribution of individual titers. The possibility was entertained that this difference might be due to a factor of time, inasmuch as patients with acute rheumatic fever are in general seen for the first time a few weeks after the onset of any preceding streptococcal infection. Although 3 weeks is generally considered an adequate period for the attainment of maximal antibody response in acute infection, a longer effective period of antigenic stimulation in the case of streptococcal hyaluronidase would be consistent with the fact that the hemolytic streptococcus produces little hyaluronidase, in comparison with other metabolic products; so much so that direct search for the enzyme in culture media led to the impression that only a few strains of the organism produce the enzyme.[1,9] (This is in contradistinction to the hemolysin, which is readily found in streptococcal culture filtrates.)

In order to examine the validity of such an explanation, sera were collected from as many of the convalescents of scarlet fever as possible, after an additional interval of 3 weeks. A comparison of anti-hyaluronidase titers at this time, 6 weeks after the onset of the illness, with those taken at the time of convalescence showed that some of these children, slightly less than half, had higher titers at the 6th week than at the third. The mean antibody titer of these 6th-week specimens was 120 which, although higher than the mean of 73 in the 3rd week, was approximately one-fifth the mean titer found in acute rheumatic fever. In the 5th month after the onset of scarlet fever the mean anti-hyaluronidase titer had returned to the value which obtained in the 3rd week.

It is thus quite unlikely that the factor of time accounts for the difference between anti-hyaluronidase titers of convalescents from streptococcal infection and patients with acute rheumatic fever. Since no chemotherapy was given to the patients with scarlet fever it was not necessary to consider such a factor as a possible cause of the lower

range of titers in the convalescents from scarlet fever in comparison with the acute rheumatic group. Since work now in progress indicates that antibody levels to the other streptococcal antigens under investigation in these laboratories do not show such marked differences between the convalescents from scarlet fever and the acute rheumatics, this work raises the possibility that hyaluronidase, or strains or variants of streptococci producing unusual amounts of hyaluronidase, may be related in some way to the pathogenesis of rheumatic fever. The necessarily indirect method of investigating such a relationship—that of measuring antibodies to hyaluronidase rather than the enzyme itself—may represent a limitation in demonstrating an entirely clear-cut distinction with respect to hyaluronidase between patients with rheumatic fever and those with streptococcal infection. On the basis of the results reported it is impossible to say whether there exists a special relation of streptococcal hyaluronidase to rheumatic fever. Such a relation is, however, a possibility which cannot be excluded in the face of these data.

Diagnostic Applications of the Streptococcal Anti-Hyaluronidase Test. Aside from considerations of a possible role of anti-hyaluronidase in the pathogenesis of rheumatic fever, the question arises of its usefulness in the laboratory diagnosis of rheumatic fever. This test suffers the same shortcoming in this regard as do other tests for antibodies to streptococcal antigens: the fact that not all titers found in acute rheumatic fever fall out of the entire range of titers found in the presumably normal population. However, two aspects of this neutralization test remain to be explored. First, the sensitivity of the anti-hyaluronidase test as compared with tests for antibodies to other streptococcal antigens, in correlation with variations in clinical phase of the disease and, second, the possibility that simultaneous performance of the anti-hyaluronidase test and one of these other tests may yield more striking differences between normal subjects and patients with active rheumatic fever than any one test alone. These questions are now under investigation, the results of which will be reported elsewhere.[3]

Summary. The mucin-clot prevention test for the measurement of hyaluronidase *in vitro* has been applied to the measurement of neutralizing antibodies to streptococcal hyaluronidase in serum. The reliability of this test has been confirmed by comparison with spreading potency of the hyaluronidase in the skin, and the specificity of the test for enzyme of streptococcal origin has been confirmed by comparative tests with pneumococcal, clostridial and testicular hyaluronidase.

Streptococcal anti-hyaluronidase has been found in the sera of presumably normal human beings: at mean titers of 46 in neonatal infants, less than 8 in infants, 36 in children, and 30 in young adults.

In a typical acute streptococcal infection, scarlet fever, the mean anti-hyaluronidase titer in 130 individuals was found to be 73 at the third week after the onset of the illness, in comparison with 20 during the first few days. In some children the titer continued to rise after the 3rd week.

In patients with quiescent rheumatic fever the findings were comparable to those in normal children. In 100 patients with acute rheumatic fever, however, the geometric mean titer was 580, 84% of the individual titers being higher than the entire range found among quiescent rheumatics.

The possible implications of these findings are discussed in terms of the epidemiology of streptococcal disease

and the serologic diagnosis of acute rheumatic fever.

NOTE: Since this report has gone to press a paper has appeared in which it was found that the mean titer to streptococcal hyaluronidase in sera of patients with rheumatic fever was significantly higher than the mean titer in sera obtained from convalescents of streptococcal infections, other infections and normal individuals.[16]

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ALLERGIC CARDIOVASCULAR DISEASE, WITH REPORT OF TWO CASES OF PERIARTERITIS NODOSA

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The concept of a single basic pathologic process producing a variety of syndromes has increasingly occupied medical thought since Philippe Ricord[26] corresponded with the Union Medicale on syphilis. Ricord recognized that the reaction of a tissue to a specific agent may vary widely and believed that functional impairment is more dependent on the organ involved and magnitude of the involvement than on the agent producing the damage. The first of these concepts, variability of tissue response to a specific injurious agent, was greatly elucidated by the studies of Opie[20] and of Rich[22] in their investigations of allergic inflammations to determine local tissue injury and reaction.

It has become equally well established that different injurious agents can cause the same type of tissue reaction. Widespread vascular lesions have in recent years been noted as prominent features of such diseases of obscure etiology as periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus, thrombo-angiitis obliterans, and diffuse scleroderma. The fibrinoid degeneration occurring in each has suggested a common basic factor in etiology (Banks[3], Klemperer, Pollack, and Baehr[17]). Since this alteration of connective tissue appears identical to that seen in serum sickness, in the Arthus phenomenon, in drug sensitivity, and in experimental protein hypersensitivity, there has been much discussion as to whether the supposed common factor is one of allergy. Baehr and Pollack[2] in a critical analysis point out that since fibrinoid degeneration represents only a diffuse injury of unknown nature, it cannot be used as evidence that the reaction in all cases is one of hypersensitivity. Klemperer[16] likewise has warned against use of the argument that a related pathogenesis is indicated by the morphological similarity of lesions, which was excellently demonstrated in a recent study by Bergstand.[4]

Periarteritis nodosa is the disease of this group in which the evidences of an allergic antecedent have been best demonstrated. Since first suggested by Gruber[11] in 1923, the appearance of allergic manifestations in many periarteritis nodosa victims and the presence of eosinophils in the lesions have favored the probability of hypersensitivity in its pathogenesis. Although eosinophilia was recorded in only 19% of 101 cases collected by Harris, Lynch, and O'Hare[14], it is frequently transient and may be missed unless many blood examinations are made. Bronchial asthma was noted in 18% of 300 cases of periarteritis nodosa analyzed by Wilson and Alexander[27]. When other atopic disorders like vasomotor rhinitis and urticaria were included, the

incidence of atopy in this disease was increased to 25%. Additional evidence was provided by the observations of Rich[23,24], who found lesions of periarteritis nodosa in autopsies of patients who shortly before death had become sensitized to serum, to sulfonamides, and to iodine. Rich and Gregory[25] were able experimentally to produce typical lesions in rabbits by injections of sterile horse serum. However, Alston, Cheng, and Short[1] failed to duplicate these lesions in their rabbits, using a similar procedure.

As emphasized by Harkavy[13], periarteritis nodosa seems to represent an advanced phase of hyperergic vascular disease. The nature of the sensitizing allergen is of therapeutic importance, because desensitization to the antigen or its removal would appear a possible method to halt the process. Although drugs and sera have been shown capable of producing periarteritis nodosa, in the majority of cases no such factor can be determined. Reimann, Price, and Herbut[21] suggested hypersensitivity to the trichina antigen as the basis of development of lesions in 2 cases occurring in trichinosis. Contratto[7] believed one of his cases to be the result of allergic response to active glandular tuberculosis. Bacteria are considered the most frequent sensitizing agent, and periarteritis nodosa has been observed to follow infections with various bacteria, particularly hemolytic streptococci. In such cases Miller and Daley[19] believe it is rational to employ antibiotics to eliminate the causative agent and perhaps produce a cure.

The disease has been regarded as usually fatal, but this view may well be due to the fact that most cases have been recognized at necropsy and that cases diagnosed during life are usually far-advanced. Recovery or unusually long remission after diagnosis by biopsy has been occasionally reported (Carlin and Hicks[6], Contratto[7], Goodman[10]). There has been one apparent cure with sulfapyridine (Goldman, Dickens, and Schenken[22]).

The clinical manifestations of periarteritis nodosa depend upon the tissues embarrassed by the vascular reaction. Since the lesions occur in crops and occasionally involve only 1 or 2 systems, there may be much variation in the symptoms and signs. In 1878 Meyer[18] established the diagnostic triad of chlorotic marasmus, polymyositis and polyneuritis, and gastrointestinal symptoms. Glomerulonephritis was later added by Brinkmann[5], and cerebral and cutaneous involvement by Harbitz[12]. Familiarity with the usual manifestations as described in extensive analyses and a high index of suspicion have led to more frequent diagnoses during life. Evidences of a widespread system involvement not explainable by a single, more common, disease, or an atypical course of a suspected common condition may lead to consideration of the presence of periarteritis nodosa. If allergic manifestations are also present, the likelihood of the condition is increased. Palpable nodules along the arteries are extremely significant, but occur in a minority of cases. A positive diagnosis during life can be suspected by the clinical course, but can be made with certainty only by the microscopic examination of diseased tissue. A biopsy may be taken of affected muscle or skin, or of palpable nodules along the course of the vessels. Occasionally a diagnosis may be made in unsuspected cases by examination of tissues removed at operation when a surgical condition is simulated.

The morphology of periarteritis nodosa is a disseminated focal panarteritis, which may be spotty in its dis-

tribution. The functional pathology is that of multiple, rapidly developing occlusions of small arteries to produce widespread miliary infarcts. Periarteritis nodosa is a disease of small muscular arteries, and characteristically spares the large elastic arteries and the arterioles. The process involves all coats of the vessels, but begins with a coagulation necrosis of the muscular media. The initial medial degeneration is followed by a thrombosis and neutrophilic leukocytic congregation. There then develops a subacute granulomatous inflammation, sometimes with numerous eosinophilic leukocytes among the lymphocytes, neutrophils, and histiocytes. The last stage in the primary lesion is a chronic productive inflammatory reaction with eventual canalization of some of the vessels. The changes in the surrounding tissues supplied by these vessels are successively albuminous degeneration, coagulation necrosis, and eventual replacement fibrosis. Multiple aneurysms are present in about 10% of the cases.

The following 2 cases, recently studied at our School of Medicine, are reported because they presented definite clinical evidence of hypersensitivity.

Case Reports. CASE 1. M.D., a 63 year old white housewife, was admitted to John Sealy Hospital on November 19, 1946, complaining of intermittent darting pains in her hands, feet, and back for 7 weeks. The pains had been accompanied by soreness of her tongue, and since they began, she had lost about 30 pounds in weight. There had been several episodes of fever to 102°F., each lasting several days. Her past history revealed good health until 1940, when she developed occasional episodes of right upper abdominal pain. In 1941 for the first time she began having frequent attacks of wheezing and shortness of breath. The attacks of dyspnea occurred at all times of the year, and for several months had been accompanied by symptoms of hay fever. For several years she had been on a self-imposed diet of toast, butter, and milk. Sensitivity tests done 6 months prior to admission were positive for coffee, lemon, potato, and feathers. There was no previous personal or familial history of allergy.

Examination revealed a chronically ill middle-aged female who appeared mentally dull. There was brownish pigmentation of the dorsal surfaces of the hands and elbows. The blood pressure was 148/76, pulse 90, temperature 100°F. Conjunctivae and mucous membranes were pale, and the tongue was atrophic with redness at the margins. The fundi showed some increase in tortuousity of the arteries but no nodularity. The heart was moderately enlarged to the left with soft systolic murmurs heard in the aortic and mitral areas. The lungs were clear, and abdomen negative. Arteries showed increased thickness, but no nodes or areas of tenderness. There was a moderate generalized atrophy of the musculature. Mild tenderness in the muscles and along the nerve trunks was noted. There was absence of the right biceps and left patellar reflexes, the remainder of the deep reflexes being hypoactive. No pathological reflexes were demonstrable. There was marked impairment of all forms of sensation in the extremities.

The red count was 2.47 million with 8.8 gm. of hemoglobin. The white count was 18,700, with 68% neutrophils, 15% eosinophils, 6% lymphocytes, and 11% monocytes. All subsequent counts showed 20 to 35% eosinophils. Urinalysis showed a maximum concentration of 1.018, trace of albumin, 5 to 10 red cells and 1 to 3 white cells per high power field. Occasional hyaline and coarsely granular casts were seen. Red cells were a constant feature of all urinalyses. Blood Kahn and Kolmer were negative. Stool examinations, routine agglutinations, and blood cultures were negative. Gastric analysis showed free hydrochloric acid. Non-protein nitrogen on admission was 47 mg., later rising to 78. Serum calcium was 9.2 mg., phosphorus 3.3 mg., and alkaline phosphatase 3.9 Bodansky units. Serum proteins were 6.8 gm. total, with 4.9 gm. albumin and 2.7 gm. globulin. Lumbar puncture showed pressure of 120 mm., with normal spinal fluid. Electrocardiogram revealed a right bundle branch block of the Wilson (S_1) type. A teleoroentgenogram of the chest showed marked enlargement of the transverse diameter of the heart and aortic arch. Lung fields demonstrated diffuse clouding, with mottled shadows and beading along the bronchovascular pattern. A deltoid muscle biopsy was diagnostic of periarteritis nodosa.

The patient ran a downhill course, with increasing stupor and remittent temperature. Urine output was about 500 cc. per day. She became anuric immediately after being given Diodrast intravenously for pyelography on her 10th hospital day. A skin test prior to the injection had been negative. During the next 3 days she passed a total of only 18 cc. of urine. She expired in uremia on her 13th day of hospitalization, during an attempted decapsulation of the right kidney.

Postmortem Examination: The pertinent gross necropsy findings were: 1. Multiple small hemorrhages over the anterior abdominal wall and flexor surfaces of the extremities. 2. Dilated and hypertrophied heart (430 gm.), with yellowish nodular lesions along the smaller arteries of the epicardium. 3. Scattered yellow miliary lesions of the hepatic portal triads and gall bladder serosa, and in the pancreas. 4. Swollen pale kidneys (R. 250 gm., L. 200 gm.), with many subcapsular and intraparenchymal dark-red and reddish-yellow miliary lesions. 5. Small nodular yellowish areas along the small arteries of the skeletal musculature. 6. Minute yellow areas scattered throughout the cortex, white matter, and subcortical ganglion masses of the brain. Microscopically the small yellowish areas in the various organs all were a necrotizing panarteritis in varying degrees of evolution (Figs. 1 and 2).

Case 2. A.M., a 38 year old colored farmer, entered John Sealy Hospital on August 17, 1946, because of marked respiratory distress. His illness began 5 weeks prior to admission, with dyspnea on exertion. This was followed 2 weeks later by intermittent episodes of precordial pain, each lasting from several minutes to 2 hours. A progressive dependent edema then began, and 5 days before admission there developed a massive anasarca. Since the age of 28 there had been rare episodes of mild joint pains involving the ankles and knees, not accompanied by redness or swelling. In June, 1946, there had been noted an acute dermatitis involving the nose and malar regions, which disappeared in a few days to leave areas of increased pigmentation.

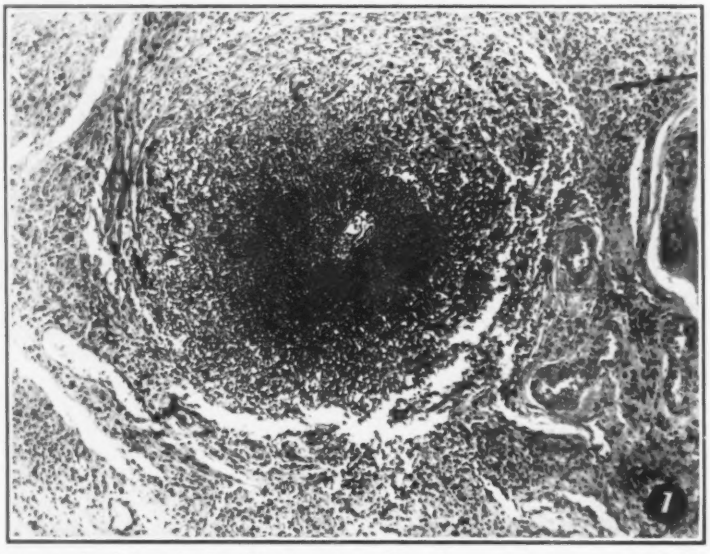

Fig. 1.–Case. 1. Small branch of pulmonary artery. Note the marked narrowing of the lumen, inflammatory reaction in all coats of the vessel, and periarterial infiltration of polymorphonuclears and eosinophils.

On examination this hyposthenic colored male was markedly dyspneic, with marked edema involving the extremities, genitalia, and trunk. The blood pressure was 170/90, temperature 102°F., and pulse 120. A paradoxical pulse was present. Both malar eminences and bridge of the nose showed irregular brownish discoloration without atrophy. There was marked distention of the neck veins, and moist rales were heard over both lung fields posteriorly. The heart was markedly enlarged, and sounds were distant. A pericardial friction rub was heard soon after admission. Neurological examination was negative.

The red count was 3.2 million with hemoglobin 64%. The white cell count was 16,400, and differential showed 91% segmenters, 4% stabs, and 5% lymphocytes. Urinalysis revealed maximum specific gravity of 1.017 and four-plus albumin. There were 50 red cells and 30 white cells per high power field. Non-protein nitrogen was 72 mg. per 100 cc; blood cholesterol, 186 mg. The sedimentation rate (Wintrobe) was 25 mm./hr. The blood Kahn was positive, and Kolmer anticomplementary. Fluoroscopy showed the presence of a pericardial effusion, and 250 cc. of blood-tinged fluid was withdrawn from the pericardium. The specific gravity of the fluid was 1.020, cultures being negative. It contained 6,850 white cells per c.mm., with a differential count of 94% polymorphonuclears and 6% lymphocytes. Electrocardiogram presented low complexes throughout, and negative T in Leads I, II, and IVF. A muscle biopsy was taken from the deltoid, and showed moderate endothelial hyperplasia of small arteries and some increase in sarcolemma nuclei. Following digitalization, low sodium diet, and diuretics, there was much improvement, and patient was discharged on October 1.

2nd Admission (18 days later): The patient was readmitted because of recurrence of dyspnea and anasarca after he discontinued his digitalis. Blood pressure was 188/108, and there was marked generalized edema. Cardiac enlargement was marked, and there were frequent moist rales at the lung bases. The red count had fallen to 1.95 million with hemoglobin 29%. The white cells numbered 8,700 per c.mm., and the differential count showed 6% eosinophils. Urinalyses were the same as previously. Non-protein nitrogen was 62 mg. The plasma proteins were 6.2 gm., with albumin 2.6 gm., and globulin 3.6 gm. Electrocardiogram showed little change. Despite redigitalization, the patient gradually became worse. On November 13 there developed many urticarial wheals over the skin of the trunk with intense itching, and these persisted 5 days. The patient subsequently developed increasing cardiac failure and expired on the 42d day of hospitalization.

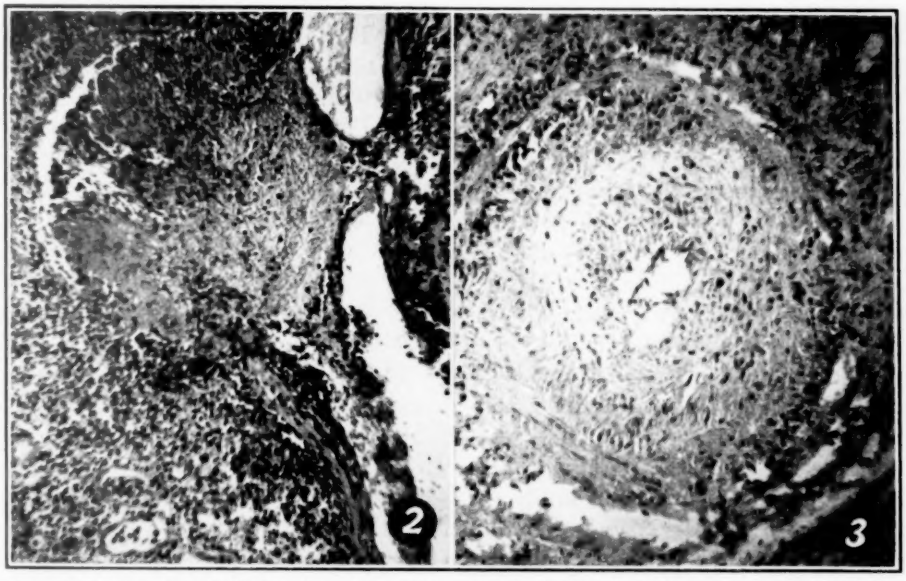

FIG. 2. Case 1. Longitudinal section of a small artery in the kidney. The changes in the vessel wall have caused a localized weakness to form a small aneurysm. There is a thrombus in the aneurysm with scattered inflammatory cells.

FIG. 3. Case 2. Small branch of coronary artery. The process is of longer duration, and fibroblastic proliferation has replaced some of the acute inflammatory reaction seen in Fig. 1.

POSTMORTEM EXAMINATION: The pertinent gross findings at necropsy were: 1. Macular pigmentation of both malar eminences. 2. Moderate edema of external genitalia and lower extremities, with 1000 cc. of clear, yellow fluid in the abdominal cavity. 3. Obliteration of pleural and pericardial cavities by thick, fibrous adhesions. 4. Heart and pericardium weighing 680 gm., with petechial hemorrhages throughout the epicar-

dium. 5. Kidneys (210 gm. each) showing numerous miliary red and yellow areas in the cortex and medulla. Microscopic examination demonstrated a conspicuous nodular panarteritis of the small arteries of the heart (Fig. 3). The myocardial stroma was edematous, and in the region of the diseased vessels was infiltrated with groups of polymorphonuclears and eosinophils. In some areas proliferating fibroblasts could be seen. The lungs showed moderate venous congestion, and the septa were thickened and infiltrated in several areas with eosinophilic leukocytes. Some of the small arteries in the lungs showed inflammation of all their coats and thrombosis. Kidneys showed hyalinization of many glomeruli, foci of chronic inflammatory cells, and replacement fibrosis.

Discussion. The first patient presents most of the clinical manifestations typically seen in periarteritis nodosa. Allergic phenomena were prominent, as evidenced by the episodes of bronchial asthma and hayfever, and a constant eosinophilia of 15 to 35%. The fever, anemia, weight loss, and weakness were conspicuous but non-specific signs. Widespread system involvement was indicated by the polyneuritis, myositis, nephritis, abnormal cardiac findings, and mental changes. The radiological manifestations in the lungs such as seen in this patient are similar to those seen in Loeffler's syndrome, and were previously described by Herrman.[15] On histological examination the pulmonary infiltrations were found to be composed of periarterial accumulations of eosinophils. The characteristic pathologic picture was demonstrated in the biopsy specimen.

Although the skin test for Diodrast was negative and there was no history of iodine sensitivity, the intravenous injection of Diodrast evidently precipitated an anuria in the previously diseased kidneys. The patient was oliguric before its administration, but was passing at least 500 cc. of urine per day of a maximum specific gravity of 1.018. Immediately after the unsuccessful attempt at pyelography, there was a sudden cessation of urine output. The total quantity of urine excreted in the 3 remaining days of life was only 18 cc. Furman[8] in a recent review of the American literature found 36 cases of fatality from the administration of 35% Diodrast, 2 of which were due to acute renal shutdown presumably caused by this drug. He emphasized the unreliability of the intracutaneous test and regarded the oral and ocular tests as more dependable. It would seem from our experience that Diodrast should be administered with caution to patients with suspected periarteritis nodosa, especially if there are indications of poor renal function or hypersensitivity. As sensitivity to iodine has been reported as actually producing periarteritis nodosa,[24] in such a situation Diodrast administration would be particularly dangerous.

The second patient represents a diagnostic problem which was solved only at necropsy. The heart and kidney were the organs predominantly involved by the pathological process, and there were clinical signs of nephritis, pericardial effusion, and cardiac failure. Arthritic symptoms such as presented by this patient are reported in 27% of the cases analyzed by Harris, Lynch, and O'Hare.[14] Allergic manifestations were transient and easily overlooked, consisting of a 6% eosinophilia on a single examination and one episode of urticaria. The endothelial hyperplasia of the small arteries in the biopsy specimen may have represented an early change of the disease, but it was not thought to be significant.

The role of the dermatitis in the disease process is difficult to evaluate because it had disappeared by the time

the patient was seen. The only residuum was a spotty hyperpigmentation of the malar eminences and bridge of the nose, and there was no evidence of scaling or atrophy. Although lupus erythematosus was considered, it was concluded from the description given that the diagnosis was most probably erysipelas. Since the symptoms began soon after the episode of dermatitis, sensitivity to the hemolytic streptococcus causing the cellulitis may well have been the etiology of the vascular reaction. It is doubted that administration of antibiotics would have been of benefit, for the dermatitis had already subsided spontaneously.

Summary: 1. The evidences for a basic factor of allergy in diffuse vascular disease of obscure origin are discussed, with particular reference to periarteritis nodosa.

2. Clinical characteristics and the pathology of periarteritis nodosa are summarized.

3. Two cases of periarteritis nodosa are reported, one of which was diagnosed during life. Sensitivity to Diodrast is regarded as the cause of acute anuria and death in the first case. In the second patient the lesions may well have developed as an allergic response to the hemolytic streptococcus. Both cases show allergic features, although in the latter they were transient.

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INCIDENCE OF THE BLOOD GROUPS AND THE SECRETOR FACTOR IN PATIENTS WITH PERNICIOUS ANEMIA AND STOMACH CARCINOMA*

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In a previous discussion of gastric cancer[1] it was suggested by one of us (A.C.I.) that there might be a relationship between the occurrence of gastric carcinoma and the blood groups and/or Rh negativeness. Bases for this assumption were several. The agglutinogens A and B are concentrated in the gastric mucus; heredity is concerned in the determination of blood groups; it is possible that premature achlorhydria, pernicious anemia and the predisposition to cancer of the stomach are hereditary; and patients with pernicious anemia seem to be predisposed to gastric cancer. This survey of the incidence of the blood groups (O, A, A_1, A_2, B, AB, A_1B, A_2B, M, N, MN, Rh_0 positive and Rh_0 negative) as well as the secretor or non-secretor attributes, was undertaken in the attempt to determine whether any relationship existed between them and pernicious anemia and stomach carcinoma. We have further attempted to determine whether there was any relationship between the ability to secrete group specific substances in the saliva and the occurrence of pernicious anemia. The ability to secrete group specific substances in the saliva has also been correlated with the gastroscopic findings in a number of these patients with the possibility in mind that the ability to secrete these substances in the saliva might be related to the character of the gastric mucosa. The gastroscopic findings in our patients have previously been reported[2]. The blood types and secretor or non-secretor ability have also been investigated in a small group of cases of carcinoma of the stomach as part of this study.

Blood group specific substances are present in the cells of almost all organs and tissues of the body, and are also present in the body fluids of secretor individuals[8]. In man these substances occur in the blood and other body cells in combination with lipids to form alcohol-soluble compounds. In the body fluids of secretors the group specific substances are present in an uncombined water soluble form, absent in non-secretors.[8a] Bray and his co-workers[3] isolated a mucopolysaccharide from gastric mucin which gave serological reactions similar to group specific substance A. The possibility that such a mucopolysaccharide may have a protective action against the development of carcinoma of the stomach is speculative at present. Approximately 82% of all Caucasians secrete blood group specific substances in their body fluids, while 18% fail to do so.[8b] Saliva and gastric juice contain the highest concentration of these substances in secretor individuals.[8c] The ability to secrete blood group specific

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substances (the "secretor" character) is transmitted as a simple Mendelian dominant and no evidence has been found of the linkage of this character with the inheritance of any of the agglutinogens.[8d] The trait is constant, and when group specific substances are lacking in the saliva they are also lacking in all other body fluids.[8e]

In a related study by Witebsky, Klendshoj and Vaughan[10] it was concluded that the gastric juice of persons with pernicious anemia contained group specific substances in at least the same amounts as normal gastric juice, in spite of the fact that there was no free hydrochloric acid or pepsin in the specimens. They determined the occurrence of blood group specific substances in the gastric juice and saliva of 12 persons with pernicious anemia and found that 11 of the 12 were secretors and one was a non-secretor. Seven of their cases had group O, 4 group A, and 1 group AB blood.

The relationship between pernicious anemia, the concomitant atrophy of the gastric mucosa, and the predilection for the development of gastric carcinoma has been discussed by numerous authors.[5 a,b,c,d]

Material. One hundred and sixty patients with pernicious anemia, who were in regular attendance at the Anemia Clinic of the Cook County Hospital (Chicago) were used in this study. Of these, 119 were white and 41 negro. The diagnosis of pernicious anemia had been established and substantiated by the usual criteria. Five of the patients with pernicious anemia had also been found to have carcinoma of the stomach by X-ray examination, gastroscopy, and/or surgical exploration and tissue examination. These cases are included in the pernicious anemia series and are also considered with the 10 cases of carcinoma of the stomach, similarly diagnosed, but not having pernicious anemia.

We have assumed, as did Schiff,[6] that the incidence of secretors and non-secretors in group O individuals was the same as in the remainder of the population. This assumption was made because of the difficulty in preparing or obtaining an anti-O serum and for this reason, no attempt was made to test the saliva of group O individuals for the secretor trait.

Methods: Five cubic centimeters of venous blood were collected from each patient. The blood was allowed to clot in the refrigerator and later a 2% cell suspension in saline was prepared and used at once. Blood grouping was done by the standard slide method, employing 1 drop of freshly prepared 2% cell suspension in saline against an equal sized drop of Anti A and Anti B serum. Each cell suspension was separately examined to exclude autoagglutination. Readings were made at 5 minutes macroscopically and checked by means of a hand lens. All serums used for blood grouping met the requirements of the National Institute of Health.

M and N typing was also performed by the slide method.

Subgrouping individuals of groups A and AB was done on the slide by mixing 1 drop of a 2% freshly prepared cell suspension and 1 drop of absorbed B serum. Readings were made microscopically after 10 minutes of gentle agitation. The presence of agglutination indicated that the cells were of subgroup A_1, A_1B.

Rh typing was performed by the standard Rh slide method using only Anti Rh_0 (Anti D) serum.

Saliva was obtained from all patients. It was collected in test tubes, placed in a boiling water bath for 20 minutes, in order to inhibit destructive enzymes, and then refrigerated. All saliva specimens, except those from group O persons, were tested within 5 days by the inhibition of agglutination method described by Wiener.[8f] The saliva was diluted 1:10 before using and the specimen was read microscopically for agglutination after gentle agitation of the tube to dislodge the clump at the bottom. Strongly positive subgroup A_2 and group B cells were selected and used in 2% solution in saline. Serums used* for the saliva typing were prepared by preliminary saline dilution of stand-

* Prepared by a laboratory licensed by the National Institute of Health.

ard blood grouping serums, the diluted material showing a specific titre of 8 (Wiener technique) to 16 (National Institute of Health technique). The results of these tests are given in Table 1.

Findings. 1. There were fewer group O individuals who had pernicious anemia than would have been expected on the basis of group O incidence in the general population. This deviation from the normal is statistically significant and is not explained. It is not due solely to the stated predilection of the disease for Scandinavians, Irish, and English[9] for, while the Scandinavians have fewer type O individuals than the United States normal, the Irish and English show a greater percentage.[8q]

2. The percentage of white pernicious anemia patients in subgroup A_1 is greater than in the general population and this deviation is also statistically significant. However, the A_2/A_1 ratio correlates with the normal. In the negro patients with pernicious anemia, the percentages of individuals in subgroups A_1 and A_2 correlate statistically with the normal group, but the ratio A_2/A_1 is deviated in a statistically significant amount from the normal. Absorbed B serums differ greatly in titre and this could account for the variations from the normal in the subgrouping of A which we have obtained.

3. Other than the above mentioned deviations, the 160 persons with pernicious anemia fell into groups comparable with large unselected series of the United States white and negro population as regards their major, minor, and blood sub-groups, as well as their secretor and non-secretor ability.

4. The number of patients in this series with carcinoma of the stomach is small (15 patients) but seems to show a normal trend in blood groups and the distribution of the secretor trait.

5. Comparison of secretor and non-secretor individuals with regard to their gastroscopic findings revealed ap-

TABLE 1. INCIDENCE OF BLOOD GROUPS AND SALIVARY SECRETOR FACTOR IN 160 PATIENTS WITH PERNICIOUS ANEMIA (5 ALSO WITH CARCINOMA OF STOMACH) AND 10 PATIENTS WITH ONLY CARCINOMA OF STOMACH

	WHITE			NEGRO			TOTAL		CARCINOMA OF STOMACH		
	Number	%	Normal %	Number	%	Normal %	Number	%	with P.A.	without P.A.	Total
Male	61	51		14	34		75	47	4	9	13
Female	58	49		27	66		85	53	1	1	2
O	34	28	45.0 (8g)	20	48	44.2 (8h)	54	34		8	8
A	62	52	41 (8k)	16	39	30.3 (8l)	78	48	4	2	6
A_1	52	43	29	12	29	19.6	64	40	4	1	5
$\frac{A_1}{A_1}$	0.19	= $\frac{A_2}{A_1}$	= (8m)0.16	0.33	= $\frac{A_2}{A_1}$	= (8n)0.67					
A_2	10	8.3	8.9	4	9.8	6.8	14	8		1	1
B	17	14	10.0	4	9.8	21.8	21	15	1		1
AB	6	5	4.0	1	2.4	3.7	7	4.3		1	1
A_1B	4	3.3	5.2			1.6	4	2.5			
A_2B	2	1.6	1.4	1	2.4	1.1	3	2		1	1
M	40	33	(8i) 29.16	12	29	(8j) 28.42	52	33	2	6	8
N	24	20	21.26	9	22	21.94	33	20		2	2
MN	55	46	49.58	20	48	49.64	75	47	3	3	6
Rh_0 +	107	91%	(2) 85.8	39	95	(7) 91.2	146	91	4	8	12
Rh_0 neg.	12	9	14.2	2	4.8	9.8	14	9	1	3	4
Secretor	66	78	(8o) 82.0	12	57	(8p) 61.2	78	73	4	3	7
Non Secretor	19	22	18	9	43	38.8	28	27	1		1

The figures in parentheses, like the superscript numbers in the text, indicate the source in the list of references.

proximately the same percentage of gastric atrophy (either localized or generalized) in both groups (Table 2).

Conclusions. 1. The occurrence of pernicious anemia is not definitely related to the blood groups or Rh negativeness.

2. Patients with pernicious anemia secrete blood group specific substances in their saliva in the same proportion as normal individuals.

3. The percentage of secretors and non-secretors was approximately the same in pernicious anemia patients who showed gastric atrophy as it was in those who had a normal gastric mucosa.

4. Patients with carcinoma of the stomach show an approximately normal distribution of blood groups and of the secretor trait.

TABLE 2. COMPARISON OF GASTROSCOPIC FINDINGS IN SECRETOR AND NON-SECRETOR INDIVIDUALS

	Negative	Localized Gastritis	Generalized or Extensive Gastritis	Carcinoma	Polyps	Benign Ulcer	Not Gastroscoped	Gastroscoped	% showing local or generalized atrophy
Secretors (78 cases)	20	19	4	1	3	1	30	48	48%
Non-Secretors (28 cases)	8	10	2	1	0	0	7	21	57%

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THE ROLE OF PLATELETS IN THE COAGULATION OF THE BLOOD*

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With the development of means to determine prothrombin quantitatively and with the coincidental discovery of vitamin K, interest in coagulation has in recent years been centered mainly on prothrombin. Knowledge concerning the other factors such as thromboplastin, calcium and platelets has not advanced proportionally and a number of investigators either ignore these factors or complacently use, as in the case of thromboplastin, almost any type of preparation with little consideration as to its purity or potency.

The issue concerning the platelets is clear cut: either they play no direct role in coagulation, or they are the very key upon which the whole hemostatic mechanism revolves. It is the purpose of this paper to offer observations that will help to settle this basic problem.

An extensive historical discussion is dispensable since adequate reviews are available.[13,17,19] It should be mentioned, however, that both Bizzozero[1] and Hayem[6] came to the conclusion from microscopic studies that a substance is liberated from disintegrating platelets that directly participates in coagulation. Their type of study has been extended by Fonio and Schwendener[4] who agree entirely with this historic view. Morawitz[14] postulated that the platelets supplied thromboplastin, and this plausible explanation of their action gained wide acceptance. Hayem[7] made the important observation that a decrease in platelets did not affect the speed of coagulation but caused an absence of clot retraction. LeSourd and Pagniez,[11] and Bordet and Delange[2] supplied an additional important observation: namely that only intact platelets could effect clot retraction. While the majority of investigators have tacitly accepted that platelets supply thromboplastin, a few workers deny that platelets play an indispensable role in coagulation. Nolf has always maintained that all the essential agents of coagulation are present in the plasma. Lenggenhager[10] summarily dismisses the platelets as having any part in the coagulation reaction. He postulates that a substance he calls prothrombokinine is changed by contact with a foreign surface to an active form which combines with calcium and prothrombin to yield thrombin. Lozner and Taylor[12] present a similar concept except that they

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call their inactive precursor globulin substance. They state specifically: "that the effects of foreign surfaces on blood coagulation are essentially independent of the intact platelet."

When Jaques and his associates[9] introduced a new agent, a silicone, which presents a surface to which platelets do not adhere, a new approach to the study of platelets was made possible. Jaques and his coworkers were able to show that if the platelets were markedly reduced by centrifugation the coagulation time of the plasma was correspondingly increased. This was confirmed by Brinkhous[3] and Quick.[16] The latter, furthermore, showed that the prothombin consumption was almost reduced to zero in platelet-depleted plasma.

In this study the function of the platelet is studied quantitatively by varying the number of platelets without changing the environmental conditions. The effect on coagulation time, speed of clot retraction, size of clot, and consumption of prothrombin are correlated.

Experimental. Blood was obtained from young normal adults by venipuncture. The syringe and needle were coated with silicone. Great care was taken to avoid contamination with tissue juice since this contains active thromboplastin. About 50 cc. of blood were collected and transferred to silicone-coated centrifuge tubes immersed in an ice bath. The syringes were kept in ice prior to use. One-half of the blood was centrifuged for 15 minutes at 4000 r.p.m. in an angle centrifuge. The plasma was transferred by means of a silicone-coated pipette to another tube and again centrifuged for 10 minutes at high speed. The other half of the blood was centrifuged at 800 r.p.m. for 10 minutes. The platelet-rich plasma was immediately transferred to a silicone-coated test tube immersed in ice water. A platelet count was made of the high and the low centrifuged plasma by direct count using 3.8% sodium citrate as diluent. Generally fewer than 20,000 platelets per c. mm. remained in the first, but in the second plasma the count was consistently much higher than in whole blood.

The high and low centrifuged plasmas were mixed in varying proportions to a volume of 2 cc. Immediately after mixing, the test tubes were placed in a water bath at 37°C. The beginning of coagulation and of clot retraction were carefully timed. It is not possible to determine accurately the completion of coagulation, but it can be roughly estimated by the density of the clot. There is a close correlation between the number of platelets and the speed at which the clot becomes opaque. Prothombin consumption was determined by the method of Quick.[15] The prothombin time of serum obtained from hemophilic or platelet-depleted plasma is 10 to 11 seconds instead of 12 seconds obtained with normal plasma. Due to this peculiar shortening, the estimation of prothrombin in serum as per cent of normal is less accurate than in plasma. Studies made on the blood of 3 cases of thrombocytopenic purpura are included to show the possible significance of the present scheme of investigation to the problem of functional pathology of purpura.

Discussion. The results obtained in this study clearly explain why the platelets have frequently been underestimated. If one were to judge the action of the platelets in the coagulation mechanism solely on the coagulation time, completely misleading conclusions would be drawn. It will be observed that the beginning of coagulation occurs nearly as early in the plasma with few platelets as in one

with a large number. Furthermore, since coagulation begins at the top of plasma, the end point for the coagulation time is reached exceptionally early because sufficient fibrin is formed to prevent the flow of blood long before actual coagulation comes to completion. Thus, not only is the coagulation time technically unreliable and even misleading, but it is also physiologically faulty for it measures the behavior of blood under totally artificial surroundings and not how it functions in the lumen of a blood vessel after injury.

Direct observation of the progress of the clot is a fairly good guide for estimating coagulation, but it has the disadvantage that it cannot be done on whole blood and even in plasma the end point, which is uniform opacity, does not necessarily mark the completion of coagulation. Clot retraction correlates well with prothrombin consumption and with the number of platelets, as is clearly shown in Fig. 1 and Table 1. The faster clot retraction appears, the more complete is the final retraction. The process follows in the main the same pattern as coagulation; namely, a relatively long latent period followed by accelerated retraction and finally a slow tapering off.

TABLE 1. THE CORRELATION OF THE NUMBER OF THE PLATELETS, COAGULATION TIME OF PLASMA, SPEED OF CLOT RETRACTION, SIZE OF THE CLOT AND PROTHROMBIN CONSUMPTION

Tube	*1*	*2*	*3*	*4*	*5*	*6*
Number of Platelets in 1 c.mm. of plasma	26,000	44,000	72,000	96,000	128,000	240,000
Beginning of Coagulation (minutes)	3½	3½	3½	3¼	3¼	3
Completion of Coagulation (minutes)*	18	16½	16½	15½	13½	10
Beginning of Clot Retraction (minutes)	34	22	20	18	13½	10½
Serum expressed in 1 hr. (cc)	0.45	1.30	1.50	1.70	1.75	1.85
Prothrombin consumed** per cent in 1 hr.	0(10)	0(10)	0(11)	20(12)	40(14)	75(19½)
in 2 hrs.	0(11)	20(12)	30(13)	45(13½)	50(15)	78(23)
in 3 hrs.	20(12)	25(12½)	40(14)	45(14½)	55(16)	80(25)
in 24 hrs.	35(13½)	50(15)	65(18)	70(19)	75(21)	87(36)

* Total uniform opacity of plasma.
** The figures in parenthesis represent the prothrombin times of serum given in seconds. The prothrombin consumption is calculated from these figures.

Far more accurate as a quantitative test of platelet function is the consumption of prothrombin and the speed and extent of clot retraction. The greater the number of platelets the more rapid the prothrombin consumption, *i.e.* the faster the conversion of prothrombin to thrombin. Below a certain number of platelets, no consumption of prothrombin can be demonstrated. To be sure coagulation occurs, since even with extreme care some platelets disintegrate; consequently some thrombin forms, and it, being an enzyme, will in spite of its minute concentration convert a considerable quantity of fibrinogen to fibrin within the confines of a test tube. The prothrombin consumption determination is theoretically and, as will be pointed out later, practically a far more reliable measure of the true speed of coagulation than is the coagulation time as carried out by the Lee-White or the numerous related procedures.

There still exists considerable confusion concerning the meaning of clot retraction and the basic mechanism involved. Quick[17] has pointed out that a certain degree of adhesion exists between fibrin and the walls of the container. Therefore the inner force, the retraction strength, must be greater than the adhesion power if retraction is to occur. This is the case when nor-

mal blood clots in a glass test tube. Collodion on the contrary has such a great affinity for fibrin, that the retraction force is too weak to counteract this adhesion; consequently no retraction occurs when normal blood clots in a collodion-coated tube, as Hirschboeck[5] first observed.

The bulk of cells is another purely mechanical factor which influences clot retraction. Retraction is most complete in cell-free, but platelet-rich plasma. In polycythemic blood, retraction is poor even though the platelets may be above normal, simply because the relatively weak retractive force cannot cope with the large cell mass and reduce its bulk. Naturally, anemic blood shows relatively good retraction.

Clot retraction is generally held to be the same as the syneresis observed

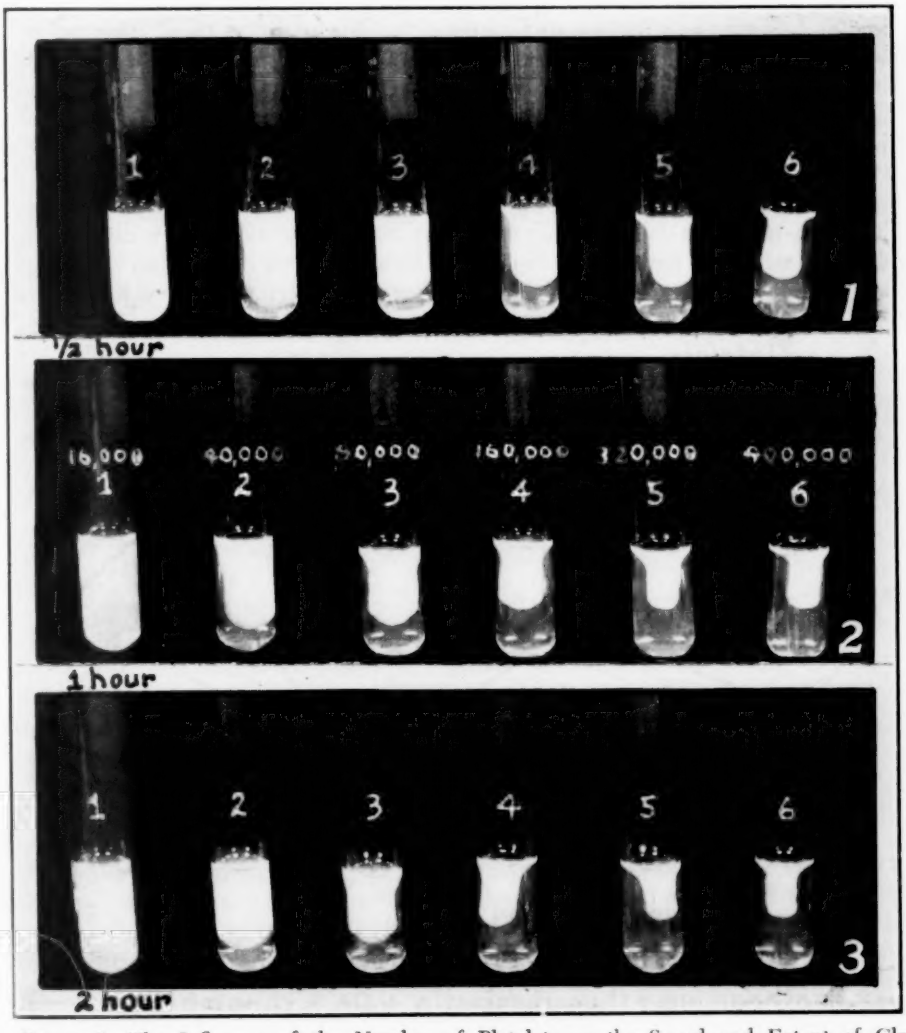

Figure 1.—The Influence of the Number of Platelets on the Speed and Extent of Clot Retraction.
The numbers on the tubes represent platelets per c. mm.

in a colloid gel, but this is probably erroneous, since it is not the completely formed fibrin gel which shrinks but rather the retraction actually occurs during the formation of fibrin. A rational explanation of the process is as follows: due to the formation of a small amount of thrombin resulting either from the rupture of a few platelets or the entrance of a trace of tissue thromboplastin into the blood, a strand or two of fibrin are formed. This immediately serves as a foreign surface on which platelets will adhere and then disintegrate. At this locus of lysis a high concentration of thrombin will form a resulting dense mass of fibrin. The new fibrin supplies again a foreign surface and the high concentration of thrombin acts as a labilizing agent on platelets with the result that the process keeps repeating itself, massing the fibrin about a small focal point, probably by twisting as Tocantins[18] suggests. When the platelets are diminished, no local areas of high concentration of thrombin occur and therefore the fibrin is evenly distributed throughout the plasma. Since the fibrin strand has no intrinsic power to contract, no shrinking of the clot can occur.

The present findings substantiate further the senior author's[15] hypothesis that the platelets on disintegration liberate an enzyme which is essential for the conversion of thromboplastinogen to active thromboplastin. The reaction between thromboplastin and prothrombin has been shown to be stoichiometric, therefore the amount of thromboplastin made available is directly measured by the prothrombin consumption test. The hypothesis previously offered

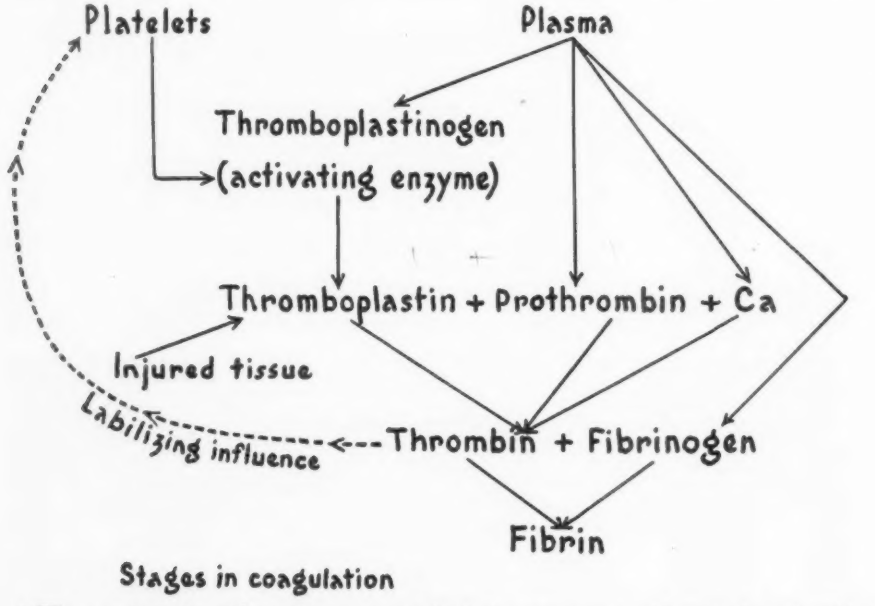

Figure 2.—A Correlation of the Factors Participating in the Coagulation Reaction.

and discussed is presented in diagram form (Fig. 2). It should again be emphasized that physiologically the first or precipitating step in coagulation may be the entrance of a minute amount of tissue thromboplastin into the blood causing the formation of a small amount of thrombin, which not only causes the formation of fibrin to which platelets adhere, but also has a labilizing action on these cells. These reasonable to conclude that the speed of prothrombin conversion determines hemostatic effectiveness, it is obvious why a diminution of platelets becomes a significant factor in producing a hemorrhagic tendency. It is also to be noted that the platelet enzyme can easily become inactivated. In fact the activation of thromboplastinogen is even incomplete in the coagulation of normal blood, and when the number of

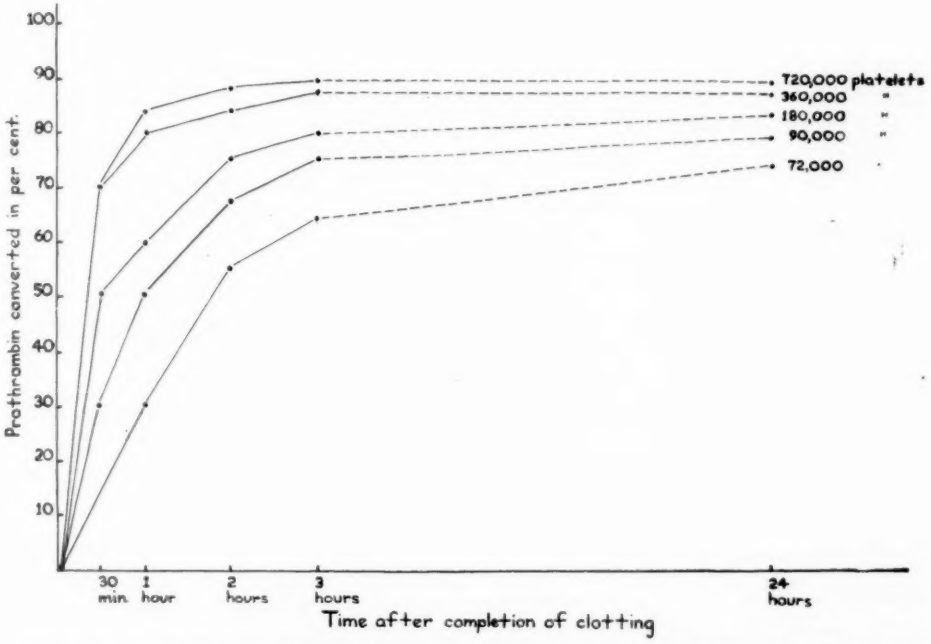

Figure 3.—The Influence of the Number of Platelets on the Speed of Prothrombin Conversion.

2 actions of thrombin cause platelets to begin disintegrating which in turn brings about the formation of more thrombin and thus sets off an autocatalytic or chain reaction.

If one constructs a graph plotting amount of prothrombin consumed against time for plasma containing varying number of platelets, a series of curves are obtained which all tend to approach a fixed final value but the speed is dependent upon the total number of platelets (Fig. 3). Since it is platelets is reduced, the amount of thromboplastin made available as measured by the prothrombin consumption test may be very small.

An explanation can now be given for the paradoxical observation that the coagulation time is generally normal in thrombocytopenic purpura. A minute amount of platelet enzyme can produce enough thrombin to coagulate sufficient fibrinogen in 5 minutes to form a clot rigid enough to give the coagulation time end-point. The clotting time

therefore is apparently normal, but this does not signify that coagulation is normal, for on determining the prothrombin consumption it is found that only a trace of prothrombin was converted during the first hour after coagulation. In Table 2 the findings of 3 cases of thrombocytopenic purpura are presented. In the 2 cases with distinct low platelet counts the coagulation was normal but the prothrombin consumption was abnormally diminished. These findings can be regarded as showing unequivocally for the first time a definite coagulation defect masked by a normal coagulation time. It will be recalled that the same occurs in hypoprothrombinemia. The normal coagulation time fails to give evidence of the basic coagulative defect of the blood. It is high time therefore for the clinician as well as the investigator to recognize the limitation of the coagulation time.

Table 2. A Correlation of Number of Platelets to Prothrombin Consumption in Thrombocytopenic Purpura

		Prothrombin Consumption in per cent of normal	
Case	*Number of Platelets in 1 c.mm.*	*1 hr.*	*2 hrs.*
1	80,000	trace (10 sec.)	trace (10 sec.)
2	29,000	trace (10 sec.)	40 (14 sec.)
3	115,000	50 (15 sec.)	60 (17 sec.)

No clot retraction was observed in Cases 1 and 2. The coagulation time was normal in all cases.

It should be noted that the second patient with a platelet count of 29,000 showed a higher prothrombin conversion than the first who had a platelet count of 80,000. This suggests that a quantitative difference in the functional activity of platelets may occur. Glanzmann[5] applied the term thrombasthenia to a condition in which platelets were normal in number, but deficient in function. His concept has remained theoretical because of the lack of experimental means to demonstrate changes in the activity of platelets. Glanzmann also postulated that platelets contain an enzyme, retractozyme, which is specifically responsible for clot retraction. This concept has never been confirmed, and it fails to explain why only intact platelets can cause clot retraction. The explanation of clot retraction offered in this paper makes it unnecessary to postulate any other factor than the enzyme which activates thromboplastinogen.

Summary. A technique was devised for varying the number of platelets without otherwise altering the plasma.

The effect of the number of platelets was studied and the following observations made: (1) The greater the number of platelets the sooner clot retraction begins, and the smaller the final clot; (2) Clot retraction is characterized by a relatively long latent period followed by an accelerated phase and protracted completion; (3) Within a wide range in the number of platelets no significant change in coagulation time can be observed; (4) As the number of platelets is diminished the speed of prothrombin consumption is decreased, but within limits the final amount of prothrombin converted approximates a fixed value; (5) Below a critical number of platelets (which varies in different bloods) the consumption of prothrombin stops after a relatively short time. This suggests that plasma contains an agent that inactivates the platelet enzyme; (6) In

thrombocytopenic purpura of sufficient severity, the consumption of prothrombin may be markedly diminished. This constitutes important evidence that a serious defect in coagulation is present which has heretofore been unrecognized because it is masked by a normal coagulation time.

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AN ELECTROPHORETIC ANALYSIS OF THE PLASMA PROTEINS IN THE AGED

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We have reported elsewhere[8,9] the fact that evidence of liver dysfunction was found in apparently normal individuals over 65 years of age when the hepatic function was tested by 5 different liver function tests. After a 5-year interval, a reinvestigation of the hepatic function in the aged was undertaken with substantially the same findings.[10] A chemical determination of the total plasma proteins and the albumin-globulin ratio by fractionation with sodium sulphate, however, failed to show any significant deviation from the commonly accepted normals.[3,4,5] It was therefore thought of interest to investigate the partition of the plasma proteins in a group of apparently normal individuals by electrophoretic analysis, since the sensitivity of the method is such that any qualitative as well as quantitative variation from the normal could be detected. To the best of our knowledge, no such study has thus far been reported.

Experimental Method. The subjects whose plasma proteins were studied comprised 21 apparently normal individuals whose age range was between 70 and 95 years. Eleven were males and 10 were females. All were ambulatory and were on the usual institutional dietary regime which has been shown to be adequate in nutritional elements.[11]

Table 1.—Electrophoretic Patterns of Plasma of the Subjects Under Investigation
(Figures represent percentage of total proteins)

No.	Age	Sex	Alb.	Alpha Glob.	Beta Glob.	Gamma Glob.	Fib.	Total Glob.	A/G
1.	70	M	61.9	6.9	16.2	10.6	4.4	33.7	1.83
2.	79	F	55.0	7.1	18.6	12.2	7.1	37.9	1.45
3.	85	F	59.0	6.2	10.0	14.0	10.9	38.2	1.95
4.	89	F	57.6	6.3	14.6	14.6	6.3	35.5	1.62
5.	70	M	59.3	7.3	14.6	12.2	6.5	34.1	1.74
6.	76	F	50.7	10.0	15.7	12.9	10.7	38.6	1.31
7.	73	M	50.7	8.0	17.4	13.4	8.8	42.2	1.18
8.	80	F	50.5	9.2	20.6	12.6	7.4	42.4	1.19
9.	81	F	62.4	12.6	8.9	9.9	6.3	31.4	1.99
10.	86	M	52.9	9.0	10.3	18.0	9.7	38.3	1.38
11.	71	F	55.2	7.8	18.2	13.0	5.8	39.0	1.42
12.	76	F	58.1	13.5	11.5	10.8	6.1	35.8	1.62
13.	77	M	53.2	12.6	9.8	16.1	8.4	38.5	1.38
14.	95	M	55.3	7.4	14.7	15.3	7.4	37.4	1.48
15.	76	F	57.8	9.7	12.2	13.0	7.3	34.9	1.65
16.	83	M	56.5	13.6	7.1	13.6	9.3	34.3	1.65
17.	78	F	50.0	12.0	14.7	14.7	8.7	41.4	1.21
18.	80	M	52.6	9.0	16.5	14.3	7.5	39.8	1.32
19.	76	F	59.3	5.9	14.5	15.8	4.6	36.2	1.64
20.	94	M	48.6	6.1	23.0	16.2	6.1	45.3	1.07
21.	70	M	47.5	9.4	16.9	15.0	11.3	41.3	1.15

The plasma was obtained with the patient in the fasting state. Sodium citrate was employed as an anti-coagulant and the cells were immediately removed after the specimen was centrifuged. The plasma was stored in a frozen state until it was ready for processing. The plasma was thawed at 0°C, diluted 1 to 4 with a buffer which was 0.02M with respect to phosphate ion, and 0.15M with respect to sodium chloride, and had a pH of 7.6. The diluted plasma was then placed inside a dialyzing membrane and dialyzed against the phosphate buffer for 8 hours, after which the buffer outside the membrane was replaced by 2 liters of fresh buffer solution, and the dialysis carried out for an additional 16 hours. This dialysis was done at a temperature of from 0 to 2°C.

The electrophoresis was carried out for approximately 3½ hours in a Klett apparatus, in a 2° water bath. Both ascending and descending Schlieren patterns were obtained. The albumin, alpha, beta, and gamma, globulin fractions were computed from the descending patterns and fibrinogen was measured on the ascending portion. This procedure was followed for purely practical purposes.

Results. The experimental findings are presented in Table 1. It may be seen from this Table that the albumin ranged from 47.5 to 62.4% of the total proteins, with an average of 55%; the globulins, exclusive of the fibrinogen, ranged from 31.4 to 45.3% of the total, with a mean of 37.9%. The fibrinogen ranged from 4.4 to 11.3%, with an average value of 7.7%. This gave an A/G ratio between 1.07 and 1.99, with a mean value of 1.4. There was no significant difference between the values for males and females. In 12 of the 21 subjects, or 57%, the albumin globulin ratio was less than 1.5. Nine of the subjects or 43%, had plasma albumin values which were less than 55% of the total proteins. In 16 of the 21 individuals, or 76%, the total globulin was more than 33% of the total proteins.

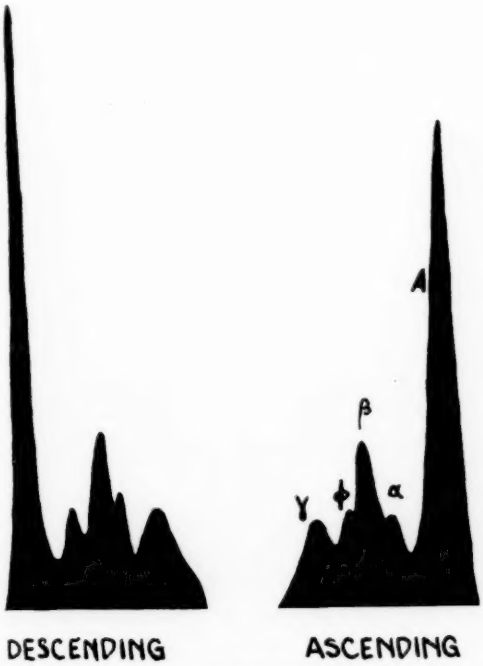

FIG. 1. *Curve* 1.—Tracing of the electrophoretic pattern from Subject 1.

The globulin fractions in the 21 subjects were as follows: (Table 1): The

alpha globulin ranged from 5.9 to 13.6% of the total protein with an average of 0.092. The beta globulin was 7.1 to 23% of the total protein with a mean of 0.148. In 14 of the 21 individuals or 67%, the beta globulin was above 14%, which was found to be the upper level in healthy young adults. The gamma globulin fraction ranged from 9.9 to 16.2% of the total protein, with an average of 0.138.

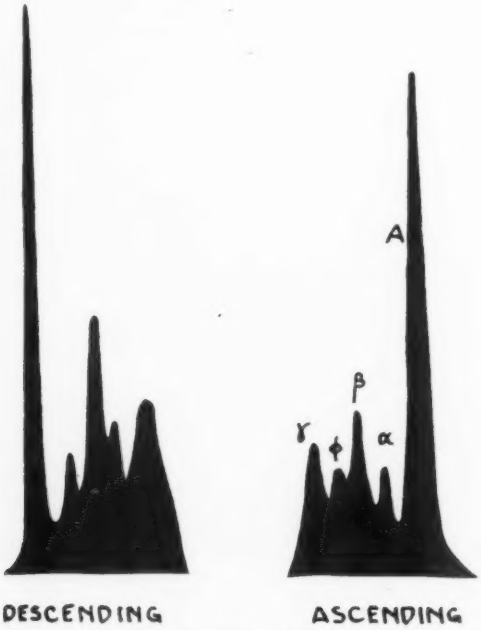

FIG. 2. *Curve* 8.—Tracing of the electrophoretic pattern from Subject 8.

Discussion. Various investigators[1,6] have undertaken to fractionate the plasma proteins in young normal adults and in patients suffering from various diseases, but to the best of our knowledge, no such study has been made of the plasma of the normal aged individuals. For this reason it is necessary to compare our findings with the results of those made in younger groups.

In Fig. 1, Curve 1, which represents a tracing of the electrophoretic pattern from Subject 1, compares favorably with the normal electrophoretic pattern which was found by other investigators. In this curve, there was found an A/G ratio of 1.83, which is a normal value. On the other hand, in the curve obtained for Subject 8, with an A/G ratio of 1.19, the pattern (Fig. 2) is somewhat different. It may be noted that the area under the curve for the globulin fraction is greater that that shown in Curve 1. In Subject 20, who had a A/G ratio of 1.07, the curve

TABLE 2.—COMPARISON OF RESULTS IN THIS STUDY WITH THOSE REPORTED FOR YOUNG HEALTHY ADULTS

Author	Alb.	Alpha Glob.	Beta Glob.	Gamma Glob.	Total Glob.	Fib.	A/G.
Martin[7]	0.58 to 0.62	0.095 to 0.14	0.11 to 0.14	0.10 to 0.14	0.31 to 0.42		1.5 to 1.9
°Leutscher[6]	0.63	0.07	0.13	0.13	0.38	0.06	1.7
°Moore and Lynn[1]	0.67	0.07	0.13	0.12	0.33		1.94
°Rafsky, Newman and Krieger	0.55	0.092	0.148	0.138	0.38	0.077	1.45

° Average values.

showed a more abnormal pattern (Fig. 3).

In Table 2 there is shown the average result for the plasma fractions reported by several investigators, as compared with the values found in this study for the older group. It will be noted that the mean albumin percentage found in this study is well below the mean albumin value reported by others. The total globulin is correspondingly higher, with the result that there is an A/G ratio lower than that reported by others for younger healthy adults.

In Fig. 4 are shown the frequency distributions for the various protein fractions. They appear to follow, on the whole, the normal distribution curve.

The average value for alpha globulin in the plasma of the subjects in this study were within the normal levels reported by other investigators. In 67% of our individuals the beta globulin were increased. It has been shown by Blix, Tiselius and Svenson[2] that the beta globulin complex contains most of the lipid carrying protein of the blood stream. With this in mind, the increase in the beta globulin fraction in the majority of apparently normal aged subjects becomes understandable, since it has been shown in a previous report[9] that the total cholesterol is elevated in most of the individuals past the age of 65 years.

The gamma globulins of the majority of the subjects appears to be within the normal limits reported by others for younger groups. This is not without possible significance, since the gamma globulins contain the antibodies to various antigens with which the individual has come in contact during his or her lifetime. It might be postulated that the subjects in our group having been exposed to various diseases over a longer period, should have a greater total amount of antibody reflected by a rise in gamma globulins. However, investigations of certain antibodies (heterophile, febrile and complement titers) by Rafsky, Silberstein

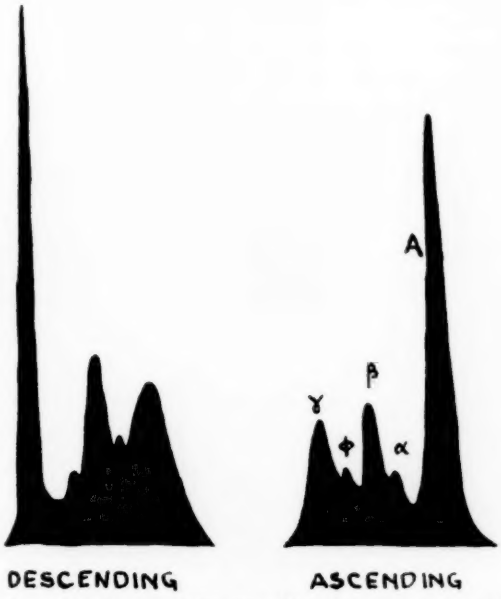

FIG. 3. *Curve* 20.—Tracing of the electrophoretic pattern from Subject 20.

and Newman,[12] have shown that in most cases, normal or even lower than normal titers of antibodies are present in the sera of normal aged subjects.

Summary. 1. An electrophoretic analysis of the plasma proteins was made in a group of 21 apparently normal aged subjects.

2. In 12 of the 21 subjects, or 57%, the albumin-globulin ratio was less than 1.5.

3. In 9 of the 21 subjects, or 43%, the plasma albumin was less than 55% of the total protein.

4. In 16 of the 21 subjects, or 76%, the total globulin was more than 33% of the total plasma proteins.

5. In 14 of the 21 subjects, or 67%, the beta globulin was higher than the upper normal levels reported for healthy young adults.

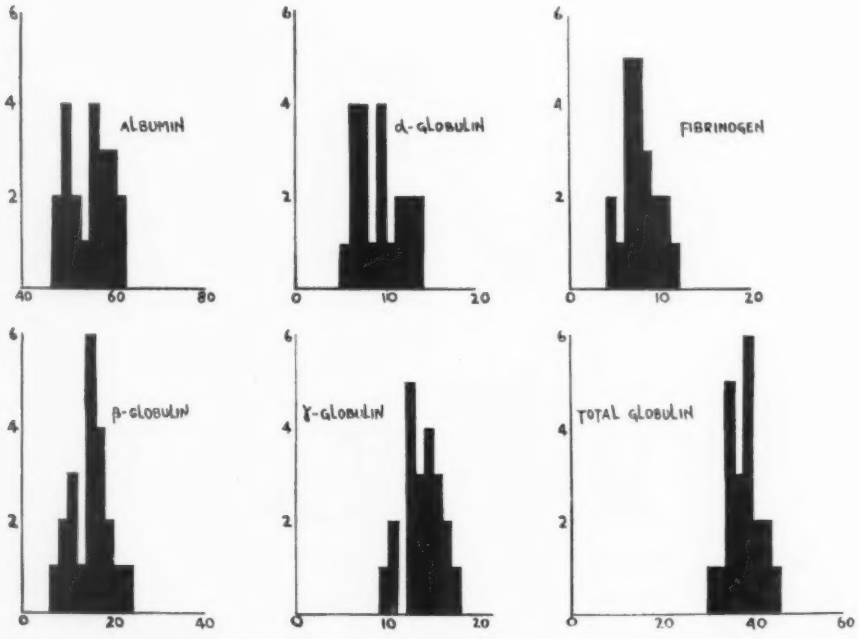

FIG. 4.–Frequency distribution for percentages of various fractions.

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THE ERYTHROCYTE SEDIMENTATION RATE IN BRUCELLOSIS*

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ACTIVE cases of human brucellosis are not readily detected. Therefore, there is need for any clinical or diagnostic procedure that will aid in the recognition of the disease. It has been stated that brucellosis may at times be differentiated from other infections because in them the sedimentation rate of erythrocytes is usually shortened[2]. Initial clinical studies in this clinic supported this statement, but with the accumulation of more data on bacteriologically proved acute and chronic cases of brucellosis, the sedimentation rate has been found to be of practically no aid, diagnostically.

Material and Methods. The findings in this report are based upon investigations in 43 human cases of brucellosis. Thirty-nine of the cases were due to *Br. abortus*, two were caused by *Br. suis*, and two by *Br. melitensis*. Fourteen of the patients had an illness of less than 3 months in duration and were regarded as acute cases, while 29 of the patients had been chronically ill for periods of 3 months to 10 years. Seven of the 35 patients, all chronic cases, had demonstrable localizing complications which included bacterial endocarditis, spondylitis, meningitis and a pericholecystic abscess. The Westergren method for measuring the sedimentation rate of erythrocytes was used in which the upper limit for normal males is 10 mm. in 1 hour, and 15 mm. in 1 hour for females.

Results. The results of the sedimentation rates were correlated with the duration of the disease, the severity of the disease, the presence of complications and the presence or absence of fever.

THE SEDIMENTATION RATE IN ACUTE BRUCELLOSIS. Fourteen cases of acute brucellosis are included in this report. It is of interest that in 9 cases the rates were accelerated, and normal in the other 5. The rate did not appear to be related to the severity of the disease. Two laboratory workers became infected with *Br. melitensis* with a demonstrable bacteremia. One individual had very minimal symptoms, which would have been entirely overlooked as being due to brucellosis under normal circumstances, but 4 determinations showed rapid rates. The second person was moderately ill, and has had 2 relapses, and yet the sedimentation rate was normal. The most rapid rate detected in all of the patients occurred in a patient who had been ill for only 3 weeks, and who made a remarkably rapid recovery following therapy with streptomycin and sulfadiazine[3].

One can only conclude from the observations made in these cases of acute brucellosis that the erythrocyte sedimentation rate is of no value in differentiating the disease from other infectious diseases.

THE SEDIMENTATION RATE IN CHRONIC BRUCELLOSIS. A total of 81 determinations were carried out in 29 patients who had had evidence of active disease for 3 months or longer. Normal rates were obtained in only 7 of the 29 subjects. The presence or absence of an accelerated rate had no relationship to the

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severity of the illness in this group of patients. Included in this group is a father and his son with chronic disease due to *Br. abortus*. The former was moderately ill, and his sedimentation rates remained normal. The son, on the other hand, was afebrile, though bacteremic, and had very little in the way of symptoms, and yet his rates were accelerated.

caused by *Br. abortus*, one had normal rates, while the other had rapid rates. The patient having the pericholecystic abscess due to *Br. suis* had rapid rates whereas the patient with meningitis due to *Br. abortus* had normal rates. In this small group of patients, then, with serious complications, the sedimentation rates were not uniformly elevated. The sedimentation rate would not ap-

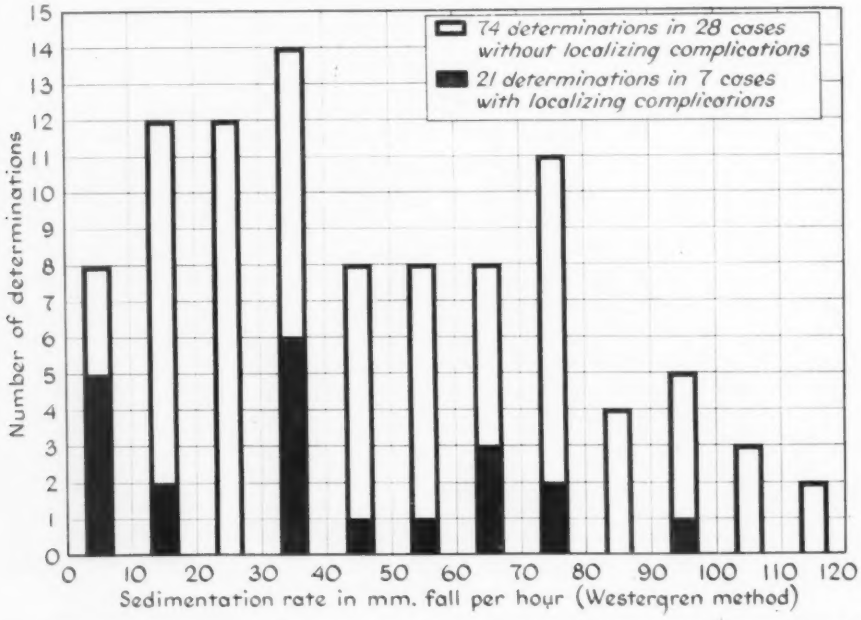

FIG. 1.—Frequency distribution of sedimentation rates in 35 cases of bacteriologically proved brucellosis. 95 determinations.

The sedimentation rate in chronic cases of brucellosis is of little practical value in the differential diagnosis of the disease.

THE SEDIMENTATION RATE IN CASES WITH DEMONSTRABLE COMPLICATIONS. Complications were observed only in 7 patients having the chronic form of the disease and included subacute bacterial endocarditis, spondylitis, meningitis and a pericholecystic abscess with abscesses of the liver. Two patients having subacute bacterial endocarditis due to *Br. abortus* had accelerated rates. Of 2 individuals with spondylitis

pear too helpful in ascertaining if complications were present.

The foregoing data have been presented graphically in Fig. 1, along with the frequency distribution of sedimentation rates in a total of 35 cases of proved brucellosis.

THE RELATIONSHIP OF THE SEDIMENTATION RATE TO FEVER. A total of 95 determinations of the sedimentation rates was made in 35 proved cases, 7 of them with localizing complications previously described, with relation to the temperatures of the patients at the time the tests were made. The informa-

tion is presented graphically in Fig. 2. There was no direct relationship observed between the height of the fever and the rapidity of the sedimentation rate.

PROGNOSTIC VALUE OF THE SEDIMENTATION RATE IN BRUCELLOSIS. Although the sedimentation rate is of little diagnostic value in brucellosis, the procedure may be of aid in interpreting the clinical course of the patient. The sedimentation rate has been helpful in ascertaining whether active disease is still present in patients who have recovered symptomatically. Although further investigations are necessary, and patients will have to be followed for a number of years, it has been observed on several occasions that as the patient assumed a state of normal health, either as a result of specific treatment or spontaneously, the sedimentation rate approached or became normal. Conversely, the patients who did not recover completely or who had relapses had consistently elevated rates. In the latter group of cases, the rapid sedimentation rates occurred in individuals who were afebrile and abacteremic, yet who were ill.

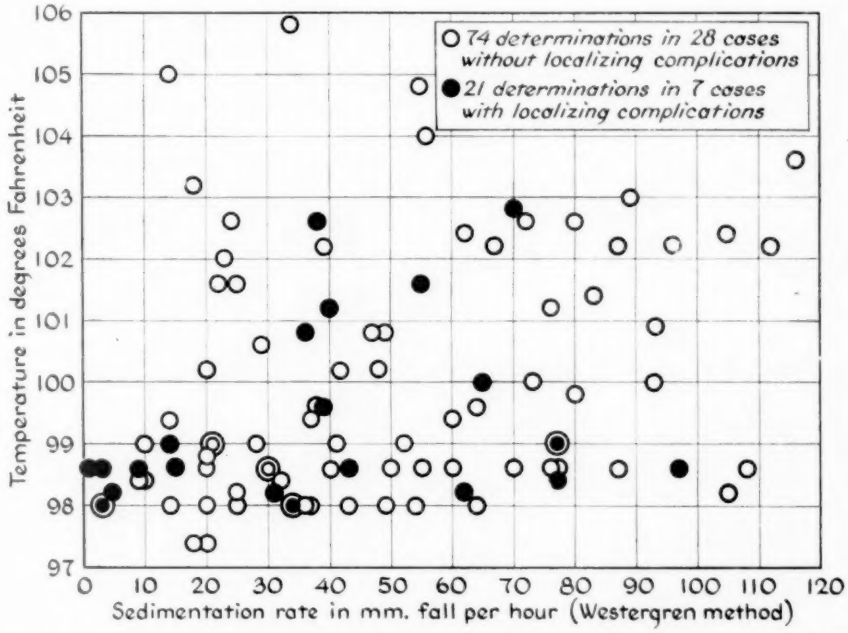

FIG. 2.—Comparison of sedimentation rate and fever in 35 cases of bacteriologically proved brucellosis. 95 determinations.

Discussion. The observations recorded in this paper indicate quite clearly that the erythrocyte sedimentation rate is of no practical value in differentiating active brucellosis from other infectious diseases. Patients quite ill with a chronic form of the disease may have normal rates, even in the presence of complications. Another chronic infectious disease with similar findings is tuberculosis.[1] Patients with extensive pulmonary tuberculosis may have normal sedimentation rates. Active rheumatic fever is another condition where normal rates may be obtained.

The sedimentation rate may be of definite aid from a prognostic point of

view in brucellosis; that is, in patients having an accelerated rate, although they are symptomatically well, there exists more of a possibility for a clinical relapse than in individuals who have recovered simultaneously with a return of the sedimentation rate to normal values. Similar observations have been made in patients with chronic disease such as tuberculosis and rheumatic fever.

Summary. 1. The erythrocyte sedimentation rate was evaluated in 43 patients having bacteriologically proved acute or chronic brucellosis. The test was found to be of little practical value in differentiating brucellosis from other infectious diseases. Normal or accelerated rates had no definite relation to the duration or severity of the illness.

2. Sedimentation rates appear to be of some prognostic help in ascertaining the presence or absence of active disease in patients who have recovered symptomatically from the disease. Persistent rapid rates appear to be associated with continued active disease.

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PROGRESS
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CARCINOMA OF THE FEMALE BREAST

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ALTHOUGH the treatment of carcinoma of the breast has undergone no radical transformation within the past few years, the disease has taken on new significance by reason of certain related developments. First, the number of patients seeking medical advice for breast symptoms has increased as a result of the concern aroused by the educational campaign of the American Cancer Society, the Public Health Service, and other agencies. The layman is becoming increasingly cancer conscious, and many women who, 10 years ago, would not have known what a lump in the breast signified or how to locate it are now thoroughly conversant with the symptoms of carcinoma and are seeking medical attention at the slightest suggestion of trouble. This means that there is now a greater opportunity to reduce the high mortality from breast cancer through early diagnosis and early treatment.

A second development which has important bearing on breast cancer is the experimental work being performed on animals. A large part of general cancer research is now directed toward mammary cancer, and recently there have been opened up new avenues of approach which may prove applicable to the problem of the control of human breast cancer. The physician will find it worth while to review briefly the existing knowledge about this important disease.

INCIDENCE. In 1946 carcinoma of the breast caused 17,500 deaths in the United States, a crude death rate of 12.5 per 100,000 persons.[18] Cancer of the breast is not as lethal as cancer in many other parts of the body. Only one-fifth of patients with breast cancer die within a year of diagnosis as compared to an average of one-third of all types of cancer.[20] Thus the prevalence of mammary cancer among the living is even more striking than its high death rate. Dorn,[21] in 1944, estimated on the basis of the urban white population that there were 108 patients

with carcinoma of the breast per 100,000 persons. Approximately 99% of all breast carcinoma occurs in females. Recent morbidity data from New York State indicate that the breast is by far the most frequent site of cancer in women, being almost twice as common as cancer of the cervix and 3 times as common as cancer of the stomach.[14,36] In 1946 the number of women dying from breast cancer was larger than from any other type of cancer, with the exception of cancer of the digestive system.[18]

The death rate from cancer of the breast increased from 10.7 per 100,000 population in 1936 to 12.5 in 1946, but these are crude death rates and do not allow for the ageing of the population during the period.[96]

Etiology of Carcinoma of the Breast. *Animal Experimentation.* A tremendous amount of work has been done on the genesis of mammary tumors in the experimental animal, especially the mouse. The work was recently reviewed by Shimkin.[85] The development of mammary cancer in the mouse appears to be controlled by the following 3 factors: (1) its genetic constitution, (2) a milk factor, and (3) hormonal stimuli.[50,85]

For many years strains of mice with a high incidence of breast cancer due to a gene or chromosomal factor have been produced by inbreeding experiments. In 1936 Bittner[9,10] discovered that the development of mammary carcinoma in mice was partly dependent on another factor, extrachromosomal, in the mother's milk. By suckling young females of a low tumor strain on mothers of a high tumor strain, the incidence of mammary carcinoma was increased. Bittner's work has been confirmed by many investigators.[7,39] By this method Haagensen and Randall[39] recently induced mammary cancer in 76% of the females of a strain of mice in which there was no mammary carcinoma among control animals. They found that as little as 0.2 cc. of milk could induce cancer. The responsible agent in the milk has not yet been identified but has been postulated to be a virus. The milk factor was not found in whole blood in significant concentrations.[33]

Lacassagne,[58] in 1932, produced breast carcinoma in male mice by the injection of large doses of estrogens. His work has been greatly extended.[29,86,90,95] Geschickter[29] reported the production of mammary cancer in 100% of nonsusceptible rats, male or female, by prolonged administration of estrogens. Shimkin and Wyman[86] found the carcinogenic dose for male mice within the ranges of concentration elaborated by the normal female of the species. The fact that carcinoma is produced not only by the naturally occurring steroids but also by synthetic estrogens with a different chemical structure suggests that estrogens are not directly carcinogenic but that they stimulate the tissues to provide a medium suitable for the development of cancer.[95]

It is difficult to assess the relative importance of the three factors—heredity, milk factor, and hormonal stimulation—because of the unsolved problems involved in an attempt to measure one independently of the others. That they do work independently is suggested by the variations which occur in the mouse's mammary gland depending on which factor is predominating.[54]

Mammary cancer has also been induced in mice by the cutaneous and intraperitoneal adminstration of methyl cholanthrene.[57,79]

Etiologic Factors of Importance in the Human. Heredity, the milk factor, and hormonal stimulation have not been proved to be of primary significance in the etiology of human cancer. In the human, hereditary factors are

probably only of importance as regards organ specificity.[14,23,71,88] McDonald[71] found that in relatives of patients with carcinoma of the breast the incidence of mammary cancer was 3 times that expected.

No evidence has yet been found of the operation of the milk factor in the human. Macklin[72] suggested that an attempt be made to trace a group of women whose mothers died in childbirth and who were not nursed by a wet nurse. A low incidence of carcinoma of the breast in such a group would suggest a direct relationship. As yet the available facts do not justify the recommendation that women with a family history of cancer should not nurse their young,[14,72] although this has been suggested.[44]

In 1944 Nathanson[74] summed up the evidence for the hormonal causation of carcinoma of the breast as follows: "Hormones may possibly be the direct cause of malignant change in the breast, either from an excess stimulation or as the result of an atypical metabolism. As yet there is not concrete evidence to prove this. It is likely that they merely prepare a substrate upon which another agent may act." For many years estrogenic hormones have been given to large numbers of women for therapeutic purposes, but only rare reports have appeared which would indicate that carcinoma of the breast might have been caused by such administration.[6,8,80] In these cases the evidence that carcinoma was produced by estrogens was not conclusive.

Two recent case reports suggest a causal relationship between carcinoma of the male breast and hormones. One man developed carcinoma following ingestion of 1,097 mg. of diethylstilbestrol over 489 days[1]; another had carcinoma of the breast associated with chorioncarcinoma of the testis.[65]

The results of animal experimentation would seem to warrant Chase's admonition[14] that "estrogens should not be given to any woman in amounts greater than normally occcurring; and none at all to women with a family history of carcinoma, especially of the breast; and none to a woman operated on for a breast tumor, before or after operation."

Childbearing and nursing apparently decrease the likelihood of the development of breast cancer.[2,14,22,71,78,88] This has given rise to the stagnation theory of causation. Adair[2] reported that only 8.5% of patients who developed mammary cancer gave a normal nursing history, whereas 80% of a control group of healthy women had nursed their children normally. For prophylaxis against breast cancer he advised that the mother nurse her children unless definite contraindications were present. If the milk factor proves to be effective in the human and if nursing is discouraged, the mother's chances of developing cancer may be increased in order to decrease those of the child.

An attempt was made to determine the effect of fertility on the age at which cancer of the breast occurs by a detailed study of 201 women treated at the Hospital of the University of Minnesota.[78] It was found that the average age of occurrence of breast cancer was the same for sterile women, those with low fertility, and those with a large number of pregnancies.

Carcinoma of the breast is most common in middle life.[76] The peak of the age incidence is between 46 and 48 years and the median age, 52. One-third of the patients are from 45 to 55 years of age.

The presence of certain benign lesions in the breast has been thought to increase the likelihood of cancer. It is probable that intraductal papilloma more than any other breast lesion predisposes to the development of cancer.[98] Exhaustive studies have been made to determine the relation of chronic

cystic mastitis to carcinoma of the breast, but the subject is still controversial. The studies of Warren[98,99] and Logie[62] suggest that there is a causal relationship. Warren's data indicate that the breast cancer attack rate for women from 30 to 49 years of age with chronic cystic mastitis is 11.7 times the rate for the Massachusetts female population. Other reports have stated that most types of chronic cystic mastitis are not precancerous.[26,30,61] Geschickter[30] stated that only in adenosis is there a significant predisposition to malignancy. It appears that the causal relationship, if it exists, is tenuous. There is general agreement that the danger of cancer is not great enough to warrant simple mastectomy in this condition for prophylactic reasons.[26,30,91,98]

Pathologic Histology. Foote and Stewart,[27] recognizing that no generally accepted classification of breast carcinoma existed, recently published the classification used at the Memorial Hospital in New York City:

Histologic Classification of Carcinomas of the Breast

I. Paget's Disease of the Nipple.

II. Carcinomas of Mammary Ducts. *(a) Noninfiltrating tumors:* 1, Papillary carcinoma; 2, Comedo carcinoma.

(b) Infiltrating tumors: 1, Papillary carcinoma; 2, Comedo carcinoma; 3, Carcinoma with productive fibrosis; 4, Medullary carcinoma; 5, Colloid carcinoma.

III. Carcinomas of Mammary Lobules. *(a) Noninfiltrating; (b) Infiltrating.*

IV. Relatively Rare Carcinomas. *(a) So-called sweat gland carcinoma; (b) Intracystic carcinoma; (c) Spindle-cell carcinoma, "adenosarcoma"; (d) Adenoid cystic carcinoma; (e) Carcinoma with osseous and cartilaginous metaplasia; (f) Squamous carcinoma; (g) Malignant variant of fibro-adenoma and cystosarcoma phyllodes.*

It is now generally thought that Paget's disease of the nipple always arises in the mammary ducts and extends to the nipple only secondarily.[15,27]

Preöperative Diagnosis. It may be stated that, in general, the easier the diagnosis of a given cancer of the breast, the less the chance of cure. Skilled observers may be able by a painstaking physical examination to differentiate a small benign from a small malignant lesion in a high percentage of instances.[36] This is probably not possible for most examiners.[25,91] What is most important is the recognition of small and indefinite "dominant lumps" and their subsequent excision for gross and microscopic examination.[89] Small axillary metastases are particularly difficult to recognize preöperatively, and nodes enlarged by benign processes are often mistaken for axillary metastases.[25,91]

In recent years, several types of benign breast lesions have been described which may give all the clinical signs of carcinoma: plasma cell mastitis,[28] granular cell myoblastoma,[40] circumscribed suppurative mastitis,[94] and comedo mastitis.[92] The fact that these lesions often cannot be differentiated from carcinoma by a preöperative examination emphasizes the necessity of biopsy before performing a radical mastectomy.

Low-Beer and his co-workers[63,64,70] of the University of California have recently reported interesting experiments on the diagnosis of breast lesions using radioactive phosphorus (P_{32}). Twenty-four or 48 hours before operation tracer doses of radioactive phosphorus were administered intravenously in the form of disodium hydrogen phosphate solution to patients with breast lesions. Skin surface measurements of radioactivity were made with the Geiger-Müller counter. Sixteen of 17 patients with benign breast lesions gave skin surface measurements comparable to those of

normal skin. Of 41 patients with malignant lesions of the breast, all but 7 showed an increase in skin surface measurements of over 25%. These 7 included very small and deeply seated lesions. Benign inflammatory lesions gave greatly increased radioactivity over the infected areas.

Roentgenography of the breast, either with or without injection of opaque material into the ducts, has been recommended as an aid in the diagnosis of breast lesions,[31,59,69] but has not generally been accepted as having much value.

Prognosis of the Untreated Patient. In 1946 Wade[97] compiled data from several reports on 777 patients with carcinoma of the breast who had had no treatment whatsoever. The average duration of life from the onset of symptoms was 38.3 months. Spontaneous cure has not been reported. In Daland's series[17] of 100 untreated patients the average duration of life after the onset of symptoms was 40.5 months, and 22% of the patients were alive after 5 years, 9% after 7 years, and 5% after 10 years.

Treatment. It is generally agreed that our present techniques of treating breast cancer are of real value in the cure of early lesions and are effective in the palliative therapy of advanced disease. In treated patients one can expect a 5 year survival of approximately 40%.[15,41,46,52] The prognosis in cancer of the breast is considerably influenced by the presence or absence of axillary metastases. If the lesion is limited to the breast, approximately 60 to 85% of patients can, with proper treatment, be expected to survive 5 years or more; whereas with axillary node involvement only approximately 25% will live 5 years.[14,30,41,46,47,52,66,69,82,88,91,93] Warren and Tompkins[100] have shown that both the cure rate and the survival time decrease as the extent of axillary metastases increases. Yet treatment is of value even in far advanced carcinoma of the breast. Wade[97] estimated that even in advanced breast carcinoma radiotherapy, alone or combined with surgery, increased the survival rate by 21.5% at 1 year, 22.5% at 2 years, 10% at three years, 10.5% at four years, and 9.5% at 5 years.

Radical mastectomy remains the treatment of choice in carcinoma of the breast. Little new has been added to its technique. The completeness with which the operation is performed is much more important than the type of operation used. This was emphasized by one study[41] in which the survival rate for radical mastectomy was in direct proportion to the duration of the operation. Not only must operation be complete, but great care must be taken not to implant cancer cells in the operative field, *i.e.* to practice "cancer asepsis".[101] Cancer has been implanted into the donor site when skin grafting has been performed in radical mastectomy.[12] Haagensen[37] has recently described his technique of radical mastectomy which emphasizes the fundamentals laid down by Halsted and Willy Meyer and includes routine skin grafting. The careful undercutting of the skin to the limits of deep removal has been advocated to decrease skin recurrences.[13] Rodman[83] attributed a low incidence of skin recurrences (2.2%) following radical mastectomy to extensive skin removal. For the surgeon who finds it necessary to ligate the axillary vein during radical mastectomy it may be of interest to note that significant edema of the arm did not follow its ligation in 4 instances.[24]

Postoperative lymphedema has been a perplexing problem for surgeons. It is most commonly caused by infection and Roentgen-ray dermatitis.[51] Guthrie and Gagnon[35] have reported an operation for the relief of lymphedema in which several collodion strips are inserted subcutaneously from the arm to the chest and left in place for 3 weeks.

In recent years there has been a tendency to limit the criteria of operability of carcinoma of the breast because of the poor results obtained in far advanced disease.[41,91] Haagensen and Stout,[41] after a careful study of postoperative results, set up the following definite contraindications to operation: 1, distant metastases; 2, inflammatory type of carcinoma; 3, supraclavicular metastases; 4, edema of the arm; 5, intercostal or parasternal nodules; 6, satellite nodules in skin over the breast; 7, carcinoma developing during pregnancy or lactation. They obtained no cures if any of these existed and regarded a patient with any of them as "categorically inoperable".

The following factors were found to signify such a poor prognosis that the presence of any two in a patient was regarded as a contraindication to operation: 1, ulceration of the skin; 2, limited edema of the skin (less than a third of the breast surface); 3, fixation of tumor to chest wall; 4, axillary nodes measuring 2.5 cm. or more in diameter and proved to contain metastases by biopsy; 5, fixation of axillary nodes to skin or deep structures with nodes proved to be metastatic by biopsy.

If these criteria were rigidly observed, the 5 year survival rate would certainly be increased, but some patients would lose the chance of cure.[46,47,52,93] The carcinoma which develops during pregnancy or lactation is not hopeless as shown by reports of long survivals following radical mastectomy in such instances.[46,47,93]

Although most observers have thought surgery to be contraindicated in inflammatory carcinoma of the breast, Meyer, Dockerty and Harrington[73] recently reported 61 patients with inflammatory carcinoma treated by radical mastectomy and postoperative irradiation. Three patients lived more than 5 years after operation, and 1 was alive 9 years after operation.

Irradiation. One of the most controversial subjects relative to breast cancer is the value of Roentgen-ray therapy as an adjunct to operation. Preöperative irradiation is rarely used in the United States, but opinions are divided concerning the usefulness of postoperative irradiation. Most observers believe that if the axillary nodes are not involved, postoperative irradiation adds little or nothing to the length of survival.[3,32,34,87] There has been great disagreement as to the value of irradiation when axillary metastases are present. Most writers have advised routine postoperative irradiation if axillary metastases are present,[3,34,45,55,56,60,66,67,68,77,82] but no very convincing statistical proof of its value has yet been given. Other authorities do not believe it is worth while except for recurrences or metastases.[38,81] As the result of a recent study at Stanford University, Siris and Dobson[87] have eliminated routine postoperative irradiation.

Irradiation is often of striking value for recurrences or metastases. Recent reports have emphasized the increase in survival as well as alleviation of suffering which irradiation affords in far advanced disease.[11,56,84,97]

Castration. Because of the possible causal relationship between estrogens and mammary carcinoma, castration has been advocated for the treatment of carcinoma of the breast of women of premenopausal age. Castration has been found to produce temporary improvement in about one-fifth of patients with metastatic carcinoma.[5,43] The greatest effect has been that on bone metastases. There seems to have been little difference in the results whether castration was by irradiation or by surgery. The value of castration as a prophylactic procedure following radical mastectomy is difficult to assess. Adair and his associates[5] advise castration for any young women of premenopausal age shown to have axillary metastases. From a study of 25 patients

treated by radical mastectomy and castration, Horsley[53] has concluded that castration is a valuable adjunct.

Hormones. During the last few years both estrogens and androgens have been shown to have beneficial effects on some patients with advanced carcinoma of the breast. Soft tissue manifestations of breast cancer are improved by administration of estrogens in about a third of patients over 60 years of age. A deleterious effect is produced in women who are menstruating.[19,42,49,75]

Androgens may affect metastases from carcinoma of the breast at any age. Testosterone is especially effective against osseous metastases but may affect soft tissue metastases in large doses.[4,48] Neither estrogens or androgens appear to have more than a temporary effect and are probably not as beneficial as Roentgen-ray therapy.[16]

Summary. Some of the recent literature concerning carcinoma of the female breast has been briefly reviewed. Although no radical changes in treatment have occurred, it is logical to expect a decrease in mortality because women with breast lumps are now reporting to physicians earlier. The physician, in turn, must excise all "dominant lumps" for gross and microscopic examination and perform a radical mastectomy if the mass proves to be cancer.

Experimental mammary carcinoma in mice is intimately related to 3 factors: heredity, the milk factor, and estrogens. As yet none of these has been proved to be of primary importance in the etiology of human mammary cancer. The preöperative diagnosis of breast lesions by the use of radioactive phosphorus, now in the experimental stage, is an ingenious new approach which may prove to be valuable.

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OPHTHALMOLOGY

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THE EFFECT OF RUTIN IN THE CONTROL OF BLEEDING INTO THE RETINA

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HEMORRHAGIC extravasations into the retina or into the vitreous or both occupy a prominent part in the ophthalmoscopic picture of many of the lesions of the internal eye which have loss of vision as their primary manifestation. In some of these lesions, the bleeding is due either to disturbances in the clotting mechanism of the blood or to defects in the vessel walls, and is the primary factor causing the disturbance of vision. In others, the bleeding is merely a secondary manifestation of an underlying inflammatory or degenerative process in the retina or choroid in which the blood vessels are involved only incidentally. In either event, the control of the bleeding is likely to seem to be the most important factor in the therapy of the retinal lesion. Therefore, the ophthalmologist seizes with avidity on any new drug recommended for this purpose. At first, such drugs are likely to be employed indiscriminately without careful consideration of the mechanism of the hemorrhage or the mode of action of the drug. Gradually, however, the use of the drug is narrowed down to use in those types of cases in which it is at least theoretically rational. This has occurred with rutin and its predecessor, hesperidin.

Hemorrhages in the retina have been noted to be associated frequently with increased fragility of the minute vessels of the skin, particularly in such disease entities as nonthrombocytopenic purpura, hypertension and diabetes mellitus. Various substances, such as citrin, hesperidin and rutin have been advocated for the treatment of such hemorrhagic conditions on the basis of their property of restoring normal capillary integrity in vessels with increased fragility. A rather voluminous literature has appeared recently.

Szent-Györgyi and associates[3] in 1936 first postulated the existence of a substance which they called "vitamin P" (permeability vitamin) on the basis of the action of an extract of Hungarian red pepper and lemon juice in cases of idiopathic or nonthrombocytopenic purpura. This extract was called "citrin" or "vitamin P," and it was suggested that a deficiency of this substance was responsible for the purpuric manifestations. From citrin later was isolated a glucoside, hesperidin, which was first reported in citrus fruits by Lebreton[28] in 1828. Studies of the properties and composition of citrin have shown it to be an impure mixture of hesperidin and eriodictyol, both of which are fla-

vanone glucosides.[24] Mager[35] in 1942 isolated eriodictyol rhamnoside from citrin, and Higby[23] from his study in 1943 of the crude flavone preparations concluded that the eriodictyol glucosides were not the source of vitamin P activity. He further found that pure hesperidin, pure limonin, or pure eriodictyol had no effect, but a substance isolated from crude orange hesperidin, identified as hesperidin methyl chalcone, was found to be active. The flavone glucoside rutin was isolated from buckwheat in 1860 by Schunck.[47] However, the properties of only one of the flavones were little known until Szent-Györgyi reported his findings. Akamatsu[2] in 1931 observed increased action of the frog heart with decreased pulse rate and increased minute volume after administration of such flavones as quercetin, quercitrin, rutin, myricetin, and myricitrin, but noted no other physiologic activity. Rutin is a rhamnoglucoside of the flavonol quercetin, having a chemical structure similar to quercitrin.[58] Couch,[21] in evaluating the capillary action of the various flavones, noted the similarity of the structure of rutin to that of hesperidin. The first studies on human beings were begun in 1942. Hesperidin decreases capillary fragility but has no effect on capillary permeability. Rutin is thought to affect both capillary fragility and permeability.

Abnormality of the capillary walls may be manifested in either or both of two ways: 1. A weak portion of the capillary may rupture with consequent extravasation of blood cells into the tissues, forming a capillary petechia. 2. Permeation of fluid may increase from the capillary into the intercellular spaces. The first abnormality is termed "increased capillary fragility" and the second is called "increased capillary permeability." In the latter condition a larger amount of protein than normal usually is released through the capillary walls. The mechanism of these disturbances is not entirely understood; but, as noted by Peck and Copley,[41] various physiologic alterations may be the basis for the pathologic manifestations. It may be that there is increased hyaluronidase activity tending to liquefy the pericapillary supporting tissue which contains hyaluronic acid. On the other hand, there may have been damage to the endothelium, resulting in inhibition of production of the intra-endothelial cement substance which may act as a protective coating for the lining of the capillary. Or there may be changes in the pericapillary elastic tissue as a result of which its cushioning effect is impaired to such a degree that application of pressure will cause rupture of the endothelium. Peck and Copley noted that this diversity of physiologic and pathologic possibilities may be responsible for the successful treatment of increased capillary fragility in one disease whereas the same treatment is ineffective in another disease in which the status of the capillaries is apparently similar.

The determination of capillary fragility is made usually by a positive pressure method, either the original supradiastolic technic of Rumpel-Leede or the infradiastolic technic of Göthlin.[17] The majority of recent authors seem to prefer the latter. For testing capillary permeability, the observation of changes in lymph flow by use of vital dyes, such as patent blue V injected intradermally, as originally devised by McMaster,[33] and successfully employed by Griffith and Lindauer,[20] is simple and adequate. Peck and Copley[41] thoroughly reviewed the various methods of testing for capillary abnormalities and gave a complete bibliography of this subject.

Capillary fragility has been found to be elevated in a host of conditions. Diem[7] tested capillary resistance of more than 500 patients by the negative pressure (suction) method of Hecht and found a lowered resistance in minor infections and intoxications, extremely low resistance in polyarthritis, moderate lowering in epidemic

hepatitis, glomerulonephritis, hepatic cirrhosis, gastric and duodenal ulcers, scarlet fever, multiple sclerosis and diabetes mellitus. A lowered content of vitamin C in the blood causes an increase in capillary fragility in scurvy.[1] This responds to the administration of ascorbic acid, but much more readily to combined treatment with ascorbic acid and vitamin P (citrin, hesperidin and rutin). However, Scarborough[45] stated that increased fragility of the capillary walls must be regarded as evidence of a deficiency of vitamin P. He described two forms of subcutaneous bleeding as a result of nutritional deficiency: (1) that caused by a deficiency of ascorbic acid, in which capillary resistance may or may not be low, but in which large ecchymoses involve the subcutaneous tissue and muscles, and (2) that caused by a deficiency of vitamin P, in which small petechiae are found in the skin. He stated that vitamin P alone does not control the large subcutaneous hemorrhages, anemia and general malnutrition characteristic of the scorbutic state, but these respond readily to large doses of ascorbic acid. But, he stated, vitamin P does benefit a lowered capillary resistance, if present in a case of scurvy.

Increased capillary fragility has not been reported in any individuals who are healthy. Cutter and Marquardt[6] stated their belief that all chronic diseases, such as rheumatic heart disease, hypertensive cardiovascular disease, diabetes mellitus and so forth, predispose to increased fragility. They found the highest degree of increased capillary fragility, as seen by capillary ruptures in the nail beds, in patients whose systolic blood pressure exceeded 200 mm. of mercury. Other conditions, associated with increased capillary fragility reported in the literature, are pulmonary hemorrhage, heart block, nuclear lesions of the eighth nerve,[49] irradiated tissues,[19] frostbite,[13] and toxic reactions due to sulfadiazine, gold salts and aspirin.[49]

That there is a high incidence of increased skin capillary fragility in hypertensive cardiovascular disease is well shown by the work of Griffith.[18] He tested 1,600 patients whose blood pressures were elevated and found that 19% had increased fragility of the capillaries and an added 11% had increased permeability of the capillaries. He noted further that 10% of those with abnormality of the capillaries had an attack of apoplexy within 16 months, whereas only 1.9% of those with normal capillaries had such an attack. Furthermore, 9% of those with damaged capillaries had subsequent retinal hemorrhages, while these were present in only 2% of those with normal capillaries. He found that 73% of the patients who had retinal hemorrhages had increased capillary fragility or permeability. Shanno and his associates[50] found that 75% of a series of 79 individuals who had hemorrhages in the retina associated with hypertension, diabetes mellitus or both had increased capillary fragility or permeability.

Since the publication of the results in the first group of patients with increased capillary fragility and permeability who were treated with rutin by Griffith, Couch and Landauer,[21] there have been many reports on its effects on various conditions. Favorable results have been reported in the treatment of gross hematuria from congenital polycystic kidneys,[11] of experimental frostbite,[13] of increased capillary fragility produced in rats by irradiation,[19] and of gastro-intestinal bleeding in hereditary hemorrhagic telangiectasia.[27] Madison and Pohle[34] stated that in 88% of 173 reported cases of purpura of various types the fragility decreased under treatment with rutin. These authors presented 14 cases of purpura in which this type of treatment gave questionable to excellent results. Stocker,[52] after investigation of the effect of rutin on the blood-aqueous

barrier, concluded that rutin causes only slight tightening of the barrier in normal rabbits, but when physostigmine is instilled into the conjunctival sac of a previously rutinized animal the increase in permeability of the barrier is much less than that which ordinarily follows instillation of physostigmine. McManus and Landrigan[32] treated 10 patients who had increased capillary fragility and 5 normal patients with from 20 to 40 mg. of rutin 3 times daily for 4 weeks with irregular results. They concluded, therefore, that rutin was ineffective in this group, but showed no toxic effects.

Concerning the treatment of the increased capillary fragility of patients with hypertensive cardiovascular disease, there have been several excellent papers, particularly those of the Griffith, Shanno, Lindauer group. This study is well summarized by Griffith.[18] Repeated studies for periods up to 48 months (average 16 months) were made on 189 patients with elevated blood pressure and with defects of the capillary walls. These patients were given initially 60 mg. of rutin each day. Tests were repeated every 6 weeks when results showed abnormal conditions and every 3 months when results were normal. The dosage of rutin was increased by 20 mg. per day whenever the tests indicated abnormalities. For 72% of the patients 60 mg. daily was sufficient to maintain capillary integrity; for 87% 80 mg. or less daily was sufficient, but 13% required varying amounts up to 400 mg. per day. In 75% of the cases results of tests became constantly normal, but in 25% they were intermittently normal. In the latter group, all but 6% of the patients were irregular in attendance for treatment and follow-up. In 16 months of observation it was found that apoplexy occurred in 1.5% of the patients in the treated group who had normal results of tests and in 9% of the group who had received irregular treatment and had had only transient periods of normal capillary resistance. The incidence of retinal hemorrhages in these two groups was the same as the incidence of apoplexy, but the retinal and cerebral lesions did not occur necessarily in the same individuals. Among 52 persons, having retinal hemorrhages, further hemorrhage occurred in 44%, 5.7% of this group had normal capillaries and 38.3% had an abnormal condition of the capillaries under treatment. It was found that treatment with thiocyanate increased the capillary permeability and capillary fragility in 8% of those treated. Madison and Pohle[34] reported questionable results from rutin therapy of 1 hypertensive patient with retinal hemorrhages. Goedbloed[16] described a patient whose petechial index returned to normal in 8 weeks with concomitant disappearance of retinal hemorrhages. Zfass[60] reported 4 cases of hypertensive cardiovascular disease with rapid clearing of retinal hemorrhages in 3 when increased capillary fragility was restored to normal. He noted with the administration of rutin the restoration to normal of capillary fragility which had been increased by thiocyanate therapy.

Donegan and Thomas,[10] treating with rutin 81 patients having increased capillary fragility, noted that there was some decrease in general capillary fragility in all. Two patients with occlusion of branches of the central retinal vein obtained no improvement with rutin therapy, while in a third patient there was marked improvement coincident with decrease in capillary fragility. Treatment with rutin was unsuccessful in 3 patients with high myopia and macular hemorrhages, in 3 patients with central choroiditis, and in 2 patients with disciform degeneration of the macula. Three patients with Eales' disease were treated with rutin. One of these showed marked improvement, 1 noted no change, and the third had a recurrence of hemorrhage into the vitreous while under treatment. They noted improvement in the retinal status

in "numerous instances" in their series of 20 patients with hypertension and various retinal complications. These authors also found complete disappearance of macular edema in 2 patients treated with rutin.

Soloff and Bello[51] conducted a study designed to recheck the results of capillary fragility tests in cases in which blood pressure was elevated and the presence of subclinical scurvy had been excluded. For this purpose, they administered 50 mg. of ascorbic acid, 50 mg. of niacinamide, 5 mg. of thiamine chloride and 3 mg. of riboflavin 3 times daily to each individual for 1 month before the tests were made. Twenty-five nonhypertensive and 50 hypertensive patients were studied. Among the 25 nonhypertensive patients, only 1, a diabetic patient, reacted positively to the Göthlin and Rumpel-Leede tests. Among the 50 patients with elevated blood pressure, only 2 gave positive reactions to the Göthlin test. One of these had diabetes. In 33 of these 50 cases (66%) results of the Rumpel-Leede test were positive. These authors stated that: "It is noteworthy that 3 of our 9 patients with retinal hemorrhages gave a negative Göthlin and Rumpel-Leede reaction . . . . There is obviously no correlation between a positive Rumpel-Leede reaction and the presence of retinal hemorrhages, as over 80% of our hypertensive patients with positive Rumpel-Leede reactions had no retinal hemorrhages." Soloff and Bello gave 20 mg. of rutin 3 or 4 times a day for a month to 10 of their patients who reacted positively to the Rumpel-Leede test. They noted no difference in the number of petechiae at the end of this time.

The source of the bleeding into the retina is not too clear in any of these reports on the vascular diseases. Presumptively, the hemorrhages were a part of hypertensive retinopathy and were not secondary to venous occlusion. A more definite idea as to the types of conditions treated is given in the report of MacLean and Brambel.[31]

In a series of 21 patients having vascular retinopathies, MacLean and Brambel have employed simultaneous treatment with rutin and dicumarol, on the basis that there are two chief retinal vascular problems: (1) hemorrhage following capillary weakness and (2) vascular occlusion as the result of thrombosis, periphlebitis, atherosclerosis or constriction. For the first, rutin was used, and for the second, heparin or dicumarol, because of their anticoagulant action. There were 6 cases of partial occlusion of the central vein, 5 of degenerative retinopathy, 2 of central serous angiospastic retinopathy. Treatment with both dicumarol and rutin resulted in improvement in all cases. Two patients with Eales' disease were treated with rutin only, and 2 with occlusion of a retinal tributary vein with dicumarol only; all improved. The remainder had diabetes. The authors postulate that thrombotic tendencies are inhibited by the anticoagulant with resulting increased vascular efficiency followed by clearing of the involved retina.

Many reports have been made on the successful therapy with vitamin P of hemorrhagic disorders accompanied by increased capillary fragility. There are a few reports only of therapy of retinal hemorrhages by the use of vitamin P preparations other than rutin. Hanum[22] noted that under treatment with citrin the capillary resistance of 1 patient with retinitis proliferans increased but there was no change in the eyegrounds. Rudy and associates[43] gave hesperidin to 6 patients having diabetic retinopathy and increased capillary fragility with negative results. A similar patient was treated by Kirtley and Peck[26] with hesperidin methyl chalcone with apparently negative results. Páez Allende[39] recommended vitamins C, K and P but presented no cases. Foxworthy's[12] results from use of hesperidin in diabetic retinopathy were disappointing, in that hesperidin tended to

decrease fragility but it had no effect on the retinal lesions. She subjected 85 nondiabetic patients and 69 diabetic patients without retinopathy and 44 with retinopathy to positive pressure tests and found an average time for the first appearance of petechiae to range from 4.9 minutes in the first group, to 2.36 minutes in the second group, to 1.5 minutes in the group with retinopathy. The number of petechiae which were present after 10 minutes were 14, 41 and 101 respectively. Saubermann[44] noted that with the intravenous use of 80 mg. of neohesperidin and of doses of vitamin C and calcium daily marked improvement occurred in vision in eyes in which there were old lesions of thrombotic type in the central vein, periphlebitis retinae, and Coats' disease, but no improvement in the vision when more recent lesions of the same type were present.

That diabetic retinopathy is an important part of the picture of diabetes mellitus, particularly in the cases of long duration, is shown by numerous studies. Wagener, Dry and Wilder[54] found retinopathy in 187 (17.7%) of 1,052 cases of diabetes, Waite and Beetham[55] in 18% of 2,002, Hanum[22] in 20.2% of 966 and Möllerström[37] on 5.1% of 2,166. Most authors have shown that the incidence is correlated more closely with the duration of the diabetes than it is with the age of the patient. Givner and Lodyjensky[15] reported on 128 diabetic patients who were less than 19 years of age; all 3 who had retinal changes were known to have had diabetes for 8 or more years. Wagener[53] noted an increasing incidence of retinopathy in cases of diabetes when his three series were compared. Retinopathy was present in 8.3% of the 1921 series of cases, in 17.7% of the 1934 series and in 30.6% of the 1945 series of 1,021 cases. He found retinopathy in 10.7% of patients who had had diabetes for less than one year, in 22% of those who had had it for from 1 to 10 years, in 65% of those who had had diabetes for from 11 to 15 years, in 67% of those who had had it for more than 15 years and in 73% of those who had had the disease for 20 years or more. Dolger[8] followed for 25 years or more 200 patients who had diabetes and were less than 50 years of age at time of onset and found that none escaped retinal hemorrhages, albuminuria or hypertension or all three, in varying degree.

Treatment of diabetic retinopathy has been directed along many lines. Many authors are of the opinion that the fundamental basis for the onset of retinopathy lies in the poor control of the hyperglycemia. On the other hand, Mosenthal[38] concluded that the retinal hemorrhages were on the basis of hypoglycemic reactions and advised high enough levels of blood sugar to prevent such reactions. Schneider and coworkers[46] and Schwarz[48] stated that deficient tissue protein is the cause, and they recommended high protein diets. Many attempts have been made to reverse the process in the retina by the use of the various vitamin P substances. Throughout the literature it is remarkable that when a series of patients who have increased capillary fragility and permeability are treated, those patients who have diabetes mellitus seem to be the most refractory to restoration of the capillary status to normal.

The high incidence of increased fragility, as measured on the skin capillaries in cases of diabetes, seems significant, and points toward similar pathologic alterations in the retinal capillaries. However, the mechanism of production of diabetic retinopathy is not known. The vascular changes appear to affect the venous, rather than the arterial, side of the circulation, as on opthalmoscopic examination enlarged and tortuous retinal venules are seen in many cases of diabetes. Perhaps the earliest observable change is the presence of micro-aneurysms in the capillaries of the retina as noted by Ballantyne,[4] who suggested that venous stasis was an early and essential factor in the development of diabetic retinopathy. It is possible then that capillary

fragility and permeability are increased and this increase accounts for the small hemorrhages and exudates so characteristic of diabetic retinopathy.

Most authors have noted a high incidence of capillary abnormality in patients who have diabetic retinopathy. Rodriguez and Root[42] found that 40% of 100 unselected diabetic patients had increased fragility, while 100% of 56 patients who had diabetic retinopathy had this derangement. Of the 40 unselected patients, 65% had retinopathy. Mallery[36] found increased fragility in 25% of 120 cases of diabetes and retinopathy in 25 (83%) of these. All of Hanum's 12 patients with retinitis proliferans had capillary abnormality. McFarland[39] examined 83 diabetic patients with retinopathy and found that 92% had increased capillary fragility. Beaser and associates[5] noted increased fragility in 24% of nondiabetic nonhypertensive patients with other diseases, in 53% of nondiabetic hypertensive patients, in 54% of diabetic nonhypertensive patients and in 100% of diabetic hypertensive patients. Wagener[53] quoted Foxworthy's studies on capillary fragility in cases of diabetes in which he later showed that the initial appearance of petechiae and the number of petechiae were considerably greater in diabetic patients with retinopathy than in those with normal retinas.

The treatment of diabetic retinopathy for the most part is attended by discouraging results. Dolger[9] stated, "Neither vitamin C nor vitamin P, rutin nor hesperidin influence retinal hemorrhages significantly and unequivocally. Evaluation of such therapy is difficult because of the spontaneous remissions and exacerbations displayed by these lesions. I have given up hope in the use of these substances as the results are not strikingly different from the control group." Givner[14] has made similar statements and noted that several patients have had retinal hemorrhages during the course of rutin therapy. Subconjunctival hemorrhages also have been reported.[59] In a symposium on the subject of diabetic retinopathy, Palmer[40] stated, "We have used considerable rutin. I cannot be too enthusiastic about it." Joslin[25] stated that his group was not so pessimistic as Dr. Dolger, but were rather open-minded. Dr. White[56] said that with children who have used rutin the progress of the disease in the eyes has been less rapid. Wilder[57] stated that he and his co-workers have used it in a good many cases but the results could not be interpreted. Some patients who have had untreated retinitis in diabetes have improved spontaneously. He added further that patients who have improved during the administration of rutin may have deceived his group. At present they have an impression that in some of these cases the process has been arrested and its progress delayed by the use of rutin. Goedbloed reported a case of diabetes with retinopathy and increased capillary fragility in which the skin capillaries slowly returned to normal under treatment with 80 mg. of rutin daily but in which the retinal hemorrhages remained unchanged until 2 weeks after vitamin C was given in conjunction with the rutin, and then nearly all the retinal hemorrhages cleared. Levitt, Cholst and associates[29] treated 12 patients having diabetic retinopathy with 60 mg. of rutin daily for 2 months and 120 mg. daily for another month. These patients had been saturated with ascorbic acid as they had received 100 mg. 3 times daily for 1 month prior to therapy with rutin. They found it difficult to ascribe their results to rutin therapy. Only 4 patients showed improvement in skin capillary fragility. The retinal lesions in 5 eyes improved, but 2 of these patients showed no improvement in the fragility of the capillaries of the skin, and only 2 patients showed simultaneous improvement in retinal lesions and in fragility. One of their patients had a rapid progression of retinopathy to retinitis proliferans while under rutin therapy.

Donegan and Thomas[10] studied 45 patients having diabetes mellitus. Twenty-five of these had diabetic retinopathy. Despite a reduction in the general capillary fragility, there was little or no change in the retinopathy over a period of 3 to 12 months.

Rodriguez and Root[42] treated 20 patients with diabetic retinopathy for 8 months and found no observable change in the retinas of 13, absorption of hemorrhages in the eyes of 3, additional hemorrhages in 2, and arterial thrombosis in 2 while under therapy. Only 25% of their patients showed a return of the petechial index to normal or borderline figures. Shanno and associates[50] treated 79 patients who had retinal hemorrhage (34% had diabetes, 42% had hypertensive cardiovascular disease and the etiology of retinal hemorrhage in the remainder was not stated) and found that from 50 to 70% of patients recovered normal capillary integrity under treatment with rutin. They stated that these patients usually but not invariably failed to have further retinal hemorrhages. MacLean and Brambel[31] in their series of cases included 4 patients with diabetic retinopathy, none of whom had increased capillary fragility. However, 2 were placed on treatment with dicumarol only, while the other 2 received both dicumarol and rutin. All 4 patients had improved in visual acuity and absorption of hemorrhages.

It is fairly well established by numerous investigators that rutin has the property of restoring increased fragility of the skin capillaries to normal values in a large majority of patients so afflicted. In many patients this restoration is paralleled closely by a simultaneous improvement in the clinical condition. However, in the investigation of the effect of rutin therapy on the lesions of diabetic retinopathy and of other hemorrhages in the retina, additional factors complicate the picture. It is by no means certain that increased fragility and permeability of the skin capillaries are accompanied by a corresponding dysfunction of the retinal capillaries. Much work that has been done certainly points toward that conclusion, but there are many discrepancies. Secondly, while some types of hemorrhage in the retina may be on the basis of vitamin P deficiency, there are many others which undoubtedly come from diverse other factors. Thirdly, the evaluation of clinical improvement in the retina is notoriously difficult, since superficial hemorrhages in the nerve-fiber layer of the retina may absorb spontaneously in a few days to a week, while more deeply placed hemorrhages may persist for a year or more. Moreover, hemorrhagic retinal lesions of all types are subject to frequent remissions.

It seems that the retinal complications of the diabetic are much more refractory to treatment with rutin than are some of the other types of hemorrhage in the retina. Certainly, the reports in the literature are much less enthusiastic with regard to lesions in cases of diabetes than to those in cases of hypertension and some of the purpuras. This lack of enthusiasm may be due in part to the slow course of diabetic retinopathy in the majority of cases, so that little change may be seen from month to month, while in most other types of retinopathy the hemorrhages are situated superficially so that absorption is more rapid.

Whether rutin therapy is actually of benefit in the treatment of hemorrhagic lesions in the retina cannot be answered dogmatically at this time with the material at hand. Certainly, its action on reversing increased capillary fragility in the skin and retina is not universally accepted. Furthermore, the relationships between hypertension, retinal hemorrhage and apoplexy in treated and untreated cases as reported by Griffith[18] are noteworthy, but they have not been confirmed fully by other investigators. With regard to the lesions in the retina associated with diabetes, it might be well to adopt the attitude of Rodriguez and Root.[42] They stated,

"Our studies show that capillary resistance is definitely low in practically all persons with diabetic retinitis. We suggest the desirability of further trial of this substance [rutin]. More important, however, is the possibility that through further investigation of the pharmacology of rutin, we may ascertain the indications of its early use, in the hope of preventing the capillary damage related to the retinal and perhaps other degenerative complications in subjects with diabetes of long duration."

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BOOK REVIEWS AND NOTICES

GRAY'S ANATOMY OF THE HUMAN BODY. Revised and Edited by CHARLES MAYO GOSS, M. D., Prof. of Anatomy, Louisiana State University. 25th ed. Pp. 1478; 1263 ills., mostly in color. Phila.: Lea & Febiger, 1948. Price, $14.00.

THE continued prosperity of "Gray" through 25 editions extending over 90 years is surely a record for a medical textbook. It speaks well both for the intrinsic value of the book and for the skill of successive editors in keeping it abreast of continuing advances. The return to a single editor in this edition is accompanied by a number of changes in text and illustrations, especially in the section on muscles and fasciae, where the editor could use the results of his own unpublished research. The chapter references have been considerably expanded, so as both to include a recent bibliography for each and to "introduce the names of as many contemporary anatomists as possible." (For earlier reviews see the November, 1942; the March, 1937; and the November, 1930, numbers of this Journal.) E. K.

THE CARE AND MANAGEMENT OF LABORATORY ANIMALS. Edited by ALASTAIR N. WORDEN, M.A. (Cantab.), B.Sc. (Lond.), Milford Prof. and Director of Research in Animal Health, Univ. College of Wales. Pp. 368; 70 figs. Balt.: Williams & Wilkins, 1947. Price, $8.50.

THIS book opens with a chapter on the laws which govern the use of experimental animals, with detailed discussions of construction, equipment and management, and of pests and their control in the animal laboratory. Then follow 19 chapters on as many types of laboratory animal, each containing sections on stock, breeding cages, bedding, food requirements, handling, anesthesia and euthanasia, and diseases and their control, and each ending with a well selected list of references. The common types such as guinea pigs, rabbits, rats and mice and their wild relatives are given adequate space, but in addition the wood mouse, deer mouse, cotton rat, the voles, hamsters, ferrets, hedgehogs, pigeons, canaries, amphibia and fish are considered. An appendix on statistical analysis and indices of subjects and authors complete the book. Although the book has been prepared chiefly by British experts for use in Great Britain, it will be highly valuable to all who are concerned with laboratory animals. H. R.

MATHEMATICAL ANALYSIS OF BINOCULAR VISION. By RUDOLF K. LUNEBURG, Dartmouth Eye Institute. Pp. 104; 82 figs. Princeton, N. J.: Princeton University Press, 1948. Price, $2.50.

THIS book presents a mathematical theory of visual perception. The author believes that the qualities in a particular visual sensation can be coordinated to the points of a three-dimensional geometrical manifold. The result is a geometrical map of visual sensation. An example of this is the ordinary Euclidean map of binocular vision which can be made by the intersection of two projection lines drawn from 2 fixed points in space. The base points are the centers of rotation of the eyes, and the projection lines the optical axes.

The author states that we cannot be sure that this map truly represents the sensed qualities of form and localization of objects. This would be the case if the apparent distance of any 2 sensed points were always proportional to the geometrical distance of the associated points of the Euclidean map. But this is not true. The sensed size of astronomical objects is in no way proportional to astronomical dimensions. The problem is, therefore, to find a coordination of sensed points of a visual sensation to the points of a geometrical manifold such that the apparent distance of any 2 sensed points is always proportional to the geometrical distance of the correlated points. Such a coordination is called a psychometric coordination.

This does not answer the question whether visual space is a Euclidean or non-Euclidean manifold. Environment may be explored by making physical measurements, and the space so mapped out, called the physical space, which must be distinguished carefully from the visual space. The visual and physical space may be correlated but the relation is not necessarily a one-to-one correspondence.

The author concludes that the geometry of visual space is the hyperbolic geometry of Lobachevski. Differential formula establishes a relation between the visual and the physical space. This supports the general hypothesis that for an individual observer the apparent size of a lined element is uniquely determined by its physical coordinates. Our scale of size

seems to contract certain localizations of the lined element. Such a contraction can only be understood if there is a physiologic basis for it, either in the dioptic system of the eyes, on the retina, in the transmission to the brain, or in the cortex itself.

This monograph does not attempt to make any hypothesis about the question, and is intended only for those who are thoroughly familiar with mathematical analyses. F. A.

WIDENING HORIZONS IN MEDICAL EDUCATION. Edited by JEAN A. CURREN, M.D., President and Dean, Long Island College of Medicine, and ELEANOR COCKERILL, Professor, School of Social Work, University of Pittsburgh. Pp. 228. New York: Commonwealth Fund, 1948. Price, $2.75.

THIS is a report of the Joint Committee of the Association of American Medical Colleges and the American Association of Medical Social Workers. It suggests that the medical student should be made to realize that "Man is a biological and social being, and medicine is a natural and social science. . . . The student must learn to recognize the social and environmental factors in every case. He must develop certain attitudes that will help him to establish effective and wholesome relationships with the patient and his family, and with his own colleagues. . . . This study may be regarded as an initial probing of a subject that has broad implications and many facets. It is clear that medical social teaching is undergoing rapid change and growth." Numerous detailed case reports are included in the book which illustrate the points stressed by the authors. They make recommendations for improvement in the teaching of this field.

This book will be of special value to all teachers in the fields of medicine and social work. R. B.

A SYMPOSIUM ON THE USE OF ISOTOPES IN BIOLOGY AND MEDICINE. Pp. 445; 58 ills., photographs of speakers. Madison: University of Wisconsin Press, 1948. Price, $5.00.

IN September of 1947, at a meeting sponsored by the Wisconsin Alumni Research Foundation, a group of prominent scientists discussed the advances that have been made in the application of isotopic methods to research in biology and medicine. The papers presented by 19 of these authorities are published in this book; together they comprise an inclusive review of the subject.

Eight of the articles are concerned with historical background and with a discussion of the preparation, separation, and assay of isotopes and their incorporation into compounds. Of particular interest to medical men will be the sections on the use of tracers in the study of intermediary metabolism and on the possible medical applications of these findings. In addition, there are several essays dealing with precautions to be taken in handling radioactive materials and with the subject of international control of atomic energy.

The fact that the authors are distinguished leaders in their fields strongly recommends this book to those who are interested in a general survey of the subject. It is to be regretted that the panel discussions, one of the most stimulating aspects of the Madison meeting, were not also published. M. C.

READING AND VISUAL FATIGUE. By LEONARD CARMICHAEL, Ph.D., President, Tufts College, and WALTER F. DEARBORN, M.D., Ph.D., Director, Psycho-educational Clinic, Harvard. Pp. 483; 103 figs. Boston: Houghton Mifflin, 1947. Price, $5.00.

THIS book is the outcome of a series of studies made by the authors in the laboratories of Tufts College and in the Harvard Clinic. The first chapter defines visual fatigue. Considerable space is given to a general resumé of the anatomy and physiology of the ocular apparatus. Chapter 2 deals with the mechanics of reading as a visual task. Chapters 4, 5 and 6, review the evidence demonstrating the nature of the effect certain environmental variables have upon reading behavior.

A review is then given of the various means of recording eye movements during reading, followed by the authors' own experiments. They were unable to show any fatigue on the part of a normal subject reading continuously for six hours. Similarly, they conclude that microfilm reading can be carried on for six hours without unduly fatiguing the normal subject.

The book should be valuable for those interested in the psychophysiology of reading. F. A.

THE ACUTE BACTERIAL DISEASES, THEIR DIAGNOSIS AND TREATMENT. By HARRY F. DOWLING, M.D., F.A.C.P., Clinical Prof. of Medicine, George Washington Univ. With the collaboration of LEWIS K. SWEET, M.D., and HAROLD L. HIRSCH, M.D. Pp. 465; 55 figs. Phila.: W. B. Saunders, 1948. Price, $6.50.

THIS book will be found valuable by both student and practitioner. In Part 1, the first of the book's 4 sections, there are included tables of infectious diseases characterized by

particular clinical manifestations such as fever, eruption, pharyngitis, and so on. Also in Part I, there are excellent discussions of serum therapy, sulfonamide therapy, penicillin and streptomycin therapy, in which are included indications, dosages, routes of administration, toxic manifestations and the like.

Descriptions of the diseases themselves are grouped according to the type of organism responsible—Part 2 deals with the diseases caused by cocci, Part 3 those caused by bacilli, and Part 4 those in which exotoxins are a major factor. Generally, discussions of individual diseases are concerned primarily with clinical and laboratory diagnosis and with treatment, both of which are presented very clearly and with specific directions. Etiology, pathology and pathogenesis are mentioned only briefly. Although the descriptions are not especially profound, the subject matter is quite complete and clearly expounded. A group of miscellaneous diseases, including colon bacillus infections, pseudomonas infections, glanders and botulism, is treated briefly.

There are 55 excellent color photographs and clinical records of patients, and 52 instructive tables. An adequate bibliography is included. The author has drawn heavily from his own experience and from a comprehensive examination of the literature. The book has much to recommend it to the clinician. S.E.

PSYCHOSOCIAL MEDICINE. A STUDY OF THE SICK SOCIETY. By JAMES L. HALLIDAY, M.D., Department of Public Health, Scotland. Pp. 278. New York: W. W. Norton, 1948. Price, $3.50.

THIS important book discusses the sickness of society. It looks beyond the individual patients to whom physicians devote most of their attention to the health of large groups (coal miners) or nations about which physicians must come to think if they wish to have anything to say about the world they live in. A clear diagram gives much of the writer's argument: it shows the general death rate, the tuberculosis and typhoid rates and others on a down curve from 1900 to 1939: but crossing this curve in an up-sweep are suicides, peptic ulcer, hypertensive disorders and the infertility rate. The author has comments on the biological and mechanistic viewpoints in etiology in an important first chapter, and statistics of psychosomatic medicine in Part 2. His description of the training of infants in 1890 and in 1940 should not be missed. Accounts of the epidemiology of psychosocial disorders and of the growing anxiety in the modern world are other parts of a valuable and original book. E. B.

TEXTBOOK OF ENDOCRINOLOGY. By HANS SELYE, M.D., Ph.D., D.Sc., F.R.S., Institut de Medecine et de Chirurgie experimentale, Université de Montréal. Pp. 916; 200 ills. Montreal: Acta Endocrinologica, Université de Montréal, 1948. Price, $12.80.

THIS is an authoritative and profusely illustrated textbook dealing with the clinical problems of endocrinology as well as the laboratory investigations necessary for an understanding of the fundamental basis of this large field. At the same time it is an atlas of endocrinology with the equivalent of 200 pages of half-tone engravings, drawings and other illustrative material.

The book is designed primarily for the physician and specialist in endocrinology. It attempts to cover both the clinical and theoretical backgrounds of endocrinology. The pertinent anatomy, embryology and pathology receive much attention as well as a comprehensive discussion of the biological chemistry involved. The chemistry is simply and clearly presented. Where there are questions of interpretation or differences of opinion the author presents the evidence and attempts to evaluate it.

This is a well-rounded treatise in endocrinology which could well be in the library of every physician and endocrinologist. The printers have done a superb job. S. G.

MANUAL FOR LABORATORY WORK IN MAMMALIAN PHYSIOLOGY. By FRED E. D'AMOUR and FRANK R. BLOOD. 50 Experiments, illustrated. Chicago: Univ. of Chicago Press, 1948. Price, $2.75.

THIS manual of techniques and procedures on rat physiology gives many helpful hints. The authors prefer to record results with ink-writing instruments instead of smoked drums. Each experimental procedure and operation is clearly illustrated by photographs. These are the most helpful and useful part of the book. Sample calculations are outlined. In general, each experiment can be concluded within 3 hours, though experiments on the endocrine system and on anaphylactic shock often require several weeks. The small size of the rat makes manual dexterity and sound anatomical knowledge essential. In addition, numerous delicate and specialized instruments will be required for the many different methods; and some, such as the exposure of the splanchnic nerves by the dorsal approach, seem too difficult for the beginner. R. E.

OCCUPATIONAL MEDICINE AND INDUSTRIAL HYGIENE. By RUTHERFORD T. JOHNSTONE, M.D., Consultant in Industrial Health and

Lecturer, Univ. of California. Pp. 604; 117 ills., 7 in color. St. Louis: C. V. Mosby, 1948. Price, $10.00.

This textbook of occupational disease is written with broad understanding of the problems of industrial hazards. Although comprehensive, the book is not pedantic; the practical objectives of diagnosis, protection, and treatment are always foremost. The first few chapters consist of general remarks concerning functions of the industrial physician. The remainder of the book is devoted to a systematic consideration of the various substances encountered in industry. In each instance there is a brief orientation as to the chemistry and uses of the material; then symptomatology, pathology, diagnosis, and treatment of the respective disease are discussed. Illustrative case reports and accounts of animal experimentation are included. Numerous photographs of pathological and clinical material accompany the text; a useful appendix of chemicals in common trade-name products is provided. A. R.

Diseases of the Joints and Rheumatism. By Kenneth Stone, D.M. (Oxon.). M.R.C.P. Pp. 362; 58 ills. New York: Grune & Stratton, 1947. Price, $6.50.

The author knows the field of rheumatism well. This book is one of the most concise works on the rheumatic diseases, yet presents arthritis and the related diseases in an excellent descriptive manner. Throughout are good detailed descriptions of physical findings and the chapter on How to Examine Joints is particularly commendable. It is an excellent book for students. The terminology, that of the British, at times may be a little confusing. Discussion of the treatment of Rheumatoid Arthritis is somewhat sketchy and incomplete, but is certainly not as confusing as the discussions in some larger books on this subject. The section of the book on Muscular Rheumatism contains much hypothetical material which is open to considerable argument, but which certainly is as good reasoning as that conceived with most theories on the origin of fibrositis.

This book should be on the required list for any graduate student studying the diseases of the joints. J. H.

Brief Psychotherapy. By Dr. Bertrand S. Frohman, M.D., with the collaboration of Evelyn P. Frohman. Foreword by Walter C. Alvarez, M.D. Pp. 265. Phila.: Lea & Febiger, 1948. Price, $4.00.

This book can be accepted as a practical handbook on the neuroses for the general practitioner. The psychiatrist will want to know that the author favors the ideas of Stekel.

Classification of the neuroses occupies 20 pages and a description of neurotic mechanisms takes 20 more. Etiology is given 46 pages in simple terms—"The Revolt Against The Home, School, and Church", with 100 illustrative cases in single paragraphs. Therapy in general is Active Analysis with the warning that "frank neurotic states are best left untouched by inexperienced hands". Included are 14 interesting pages on the uses of semantics in treatment.

A glossary for patients is an unusual feature. E. B.

The Spleen and Hypersplenism. By William Dameshek, M.D., and Solomon Estren, M.D. From the Pratt Diagnostic Hospital and Tufts Medical School, Boston. Pp. 50; illustrated. New York: Grune & Stratton, 1947. Price, $4.75.

Dameshek and Estren have again made available as once before, in attractive, looseleaf, monograph form, the panels they exhibited at the last annual meeting of the American Medical Association, June, 1947. In outline form are presented the demonstrated anatomy, histology and physiology of that enigmatic organ, the spleen, and the suspected hyposplenic and hypersplenic functional pathology as it occurs in human disease syndromes.

An "exaggerated splenic hormonal" inhibition of bone marrow maturation and delivery of cells is hypothesized, with prompt correction reported following successful splenectomy in selected cases. Peripheral blood and sternal marrow studies are emphasized in the differential diagnosis. The adrenalin test for the demonstration of splenic cellular hypersequestration and the histopathologic evidence of splenic reticulo endothelial cell hyperphagocytosis in many of these syndromes are minimized. This brochure is a very clear, somewhat dogmatic (because of its form and purpose), treatise on the indications and contraindications for human splenectomy in both primary and secondary hypersplenic states. C. D.

Diabetes Mellitus in General Practice. By Arthur R. Colwell, M.D., Assoc. Prof. of Medicine, Northwestern Univ. Pp. 350; 24 figs. Chicago: The Year Book Publishers, 1947. Price, $5.25.

THIS monograph contains the conventional chapters on diagnosis and treatment of diabetes and its complications. Dr. Colwell's skill as a teacher is revealed in the excellent organization of the subject and in his clear summary of the modern understanding of this disease. In the aspects of diabetes which are controversial he avoids extremes and maintains the practical clarity which the physician who is not a specialist in diabetes requires. He does not mention the use of potassium and phosphate in the treatment of acidosis, though these adjuncts now appear to merit wider use. The figures are well selected and some of the elementary tables showing the responses to treatment deserve careful study. The author's purpose that "the book's contents include the best and soundest of available insight and methods of treatment, presented from a practical standpoint and organized in such a manner that the reader who lacks experience with diabetes should have little difficulty in orientation", has been excellently fulfilled. F. L.

HALLMARKS OF MANKIND. By FREDERIC WOOD JONES, D.Sc., M.B., B.S., F.R.S., F.R.C.S., and SIR WILLIAM COLLINS, Prof. of Human and Comparative Anatomy, Roy. Coll. of Surgeons. Pp. 86; 23 illus. Balt.: Williams and Wilkins, 1948. Price, $2.50.

THIS delightful little book contains the subject matter of a Linacre Lecture and an Arris and Gale Lecture delivered in 1947. Its main thesis is that Man, considered solely from the point of view of structure, is an extremely primitive type and, though more primitive in basal structure than the living monkeys and apes, Man has his own remarkable structural specifications that distinguish him from all other Mammals and appear to be his very ancient hallmarks. The authors postulate that the emergence of the human type from a very primitive Primate form took place sufficiently far back to account for the profound differentiation that has occurred. They believe that if the Primate forms immediately ancestral to the human stock are ever to be revealed, they will be utterly unlike the slouching, hairy, "ape men" of which some have dreamed and will be found in geologic strata antedating the heyday of the great apes.

The book should be of special interest to those who assume that the use of monkeys of any sort for experimental work may be justified on the basis of a close relationship to Man. W. F.

THE THYROID AND ITS DISEASES. By J. H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University. 2d ed. Pp. 571; 63 illus. Philadelphia: J. B. Lippincott, 1948. Price, $12.00.

THE ADVENT of the 2d edition of this notable book should receive a warm welcome from all who have enjoyed the 1st, which appeared in 1937. This volume clearly reflects the tremendous advances in our knowledge of the normal and abnormal physiology of the thyroid and the treatment of its diseases during the intervening 11 years, to the development of which the author and his associates have been important contributors. There are 21 chapters dealing with the embryology, anatomy, physiology, endocrine relationships, pathology and clinical disorders of the thyroid. The chapter on Surgery of the Thyroid was prepared by Dr. Oliver Cope; those on the Pathology and Tumors of the Thyroid were written by Dr. Rulon W. Rawson.

The style is informal, sometimes almost conversational, and makes for easy reading. Throughout, the book is strongly flavored by the personality of the author; this is particularly apparent in the delightful last chapter entitled "Fact and Fancy in Matters Thyroid". There can be little doubt that this is the foremost work available in its field today, and it deserves a place on the shelf of all who are interested in thyroid disease. E. R.

CLINICAL LABORATORY METHODS AND DIAGNOSIS. By R. B. H. GRADWOHL, M.D., D. Sc., F.R.S.T.M.&H. (London), Director of Gradwohl Laboratories, St. Louis, Mo., and DR. PEDRO KOURI, Director of Tropical Medicine, Havana, Cuba. 4th ed. 3 volumes. Pp. 3291; 1111 ills., 58 in color. St. Louis: C. V. Mosby, 1948. Price, $40.00.

THE new edition of this well known treatise has been greatly expanded with 55% more text matter and 51% more illustrations. The section on parasitology and tropical medicine has been increased from 394 to 820 pages and now constitutes a separate volume. This excellent section describes over 175 parasites, protozoan and metazoan, important in human medicine, with 427 illustrations. The expanded sections on hematology and on blood transfusion are admirable. Bacteriologic applications in clinical diagnosis have been extended by 151 pages; 49 pages have been added on toxicologic technique; and a new chapter on electrocardiography is included.

Autopsy technique is not fully described in detail, but since this procedure is performed by the pathologist himself, this limitation is perhaps not important. The adaptation of photoelectric colorimetry to chemical procedures is inadequately presented and a number of other accepted improvements in chemical methods receive no mention. Quantitative methods are described throughout without any reference to the importance of evaluating quantitatively the error of measurement.

Such deficiencies, however, are far outbalanced by the great mass of well arranged and admirably illustrated information covering the field of clinical laboratory technology and interpretation.

Indexing, which occupies 175 pages, appears adequate. J. A.

NEW BOOKS

Technique of Treatment for the Cerebral Palsy Child. By PAULA F. EGEL, Children's Hospital, Buffalo. Pp. 203; 49 ills. St. Louis: C. V. Mosby, 1948. Price, $3.50.

The Story of The Johns Hopkins. By BERTRAM M. BERNHEIM, M.D. Pp. 235. Illustrated. New York: McGraw-Hill, 1948. Price, $3.50.

THE author, an early graduate of the Hopkins Medical School (1905) and long connected with it, has told in colloquial style "a human interest story with historical connotations." Sympathetic in the main, but with occasional barbed criticisms the story will be found to include enough details to provide a lively and satisfying picture of this great school and its famous men. E. K.

Medical Clinics of North America. Boston number. *"Specific Methods of Treatment."* Pp. 1159-1482. Phila: W. B. Saunders, September, 1948. Price, $15.00 a year.

AMONG the subjects considered are: Penicillin in pulmonary infections, antispasmodics and spasmodics in gastrointestinal disorders, treatment of various types of anemias, management of rheumatoid arthritis, medical management of essential hypertension, treatment of migraine, diagnosis and treatment of poliomyelitis, and treatment of rickettsial diseases. Practical aspects of management and recent developments are emphasized. There is a detailed discussion of the problem of infertility, and of the medical management of urinary calculi based upon the chemical composition of the stone. The description of the practical aspects of the care of patients with spinal cord injuries by Monroe, and of nutrition in protracted disease by Stare and co-workers are particularly interesting and useful, as is a discussion of brief psychotherapy in medical practice, and of repair solutions in acidosis and alkalosis. R. J., Jr.

A-B-C's of Sulfonamide and Antibiotic Therapy. By PERRIN H. LONG, M.D., F.R.C.P., Prof. of Preventive Medicine, Johns Hopkins Univ. Pp. 231. Phila.: W. B. Saunders, 1948. Price, $3.50.

WRITTEN for the practitioner, this book presents the author's clinical experience with sulfonamide, penicillin and streptomycin. Dosage schedules, pharmacology, and the toxic manifestations of each drug are presented for the chemotherapy of over a hundred infectious processes. There is no bibliography. G. R.

Neurosurgical Pathology. By I. MARK SCHEINKER, M.D., Univ. of Cincinnati College of Medicine. Pp. 370; 238 ills. Springfield, Ill.: Charles C Thomas, 1948. Price, $8.75.

Viral and Rickettsial Infections of Man. Edited by THOMAS M. RIVERS, M. D., Director of the Hospital, The Rockefeller Institute. Pp. 587; 77 ills., 6 in color. Phila.: J. B. Lippincott, 1948. Price, $5.00.

ANA Public Relations Workshop. By EDWARD L. BERNAYS. Pp. 32; 39 ills. New York: American Nurses' Association, 1948. Price, $2.50.

A MANUAL of practical public relations techniques for American nurses.

Medical Research in France During the War (1939-1945). 30 articles presented by JEAN HAMBURGER, Professeur agrégé à la Faculté de Médecine. Pp. 306. Illustrated. Paris: Éditions Médicales Flammarion, 1948. No price given.

" . . . some results of the scientific work accomplished by French physicians and biologists during the German occupation."

Therapy Through Interview. By STANLEY G. LAW, M.D., Minnesota Psychiatric Institute. Pp. 313. New York: McGraw-Hill, 1948. Price, $4.50.

After years of general practice, the author having become especially interested in our more common psychoneuroses, developed a unique method of studying his patients. The "interview techniques" employed are chiefly for the general practitioner, who is told in forthright simple language, "how to listen and to talk to patients," through case presentations con-

cerning wholly imaginary subjects. Psychiatrists may consider this dialogue method an over-simplification; however, professional associates are said to view the author's work with favor. N. Y.

Strabismus. A Clinical Handbook. By GEORGE J. EPSTEIN, M.D., Beth Israel Hospital, New York. Pp. 224; 123 ills. Phila.: Blakiston, 1948. Price, $5.00.

THIS is the third book to appear within the year on abnormalities of the ocular muscles, which attests to the interest in this subject. This volume summarizes the anatomy and physiology of the extra-ocular muscles and the modern conceptions of squint. While the major portions of its contents are of interest to ophthalmologists, the author's lucid style will afford the general practitioner a good working knowledge of the modern treatment of squint. It can be recommended to all interested in the subject. F. A.

Father Land. By BERTRAM SCHAFFNER, M.D. Pp. 203. New York: Columbia University Press, 1948. Price, $3.25.

THE AUTHOR, a neuropsychiatrist, served with the Information Control Screening Division of the American Military Government in Germany, and in this capacity performed psychiatric examinations and conducted psychologic tests, studies and opinion surveys among the German people. *Father Land*, a result of this experience, traces German authoritarianism to its origin in the family circle, and suggests complete re-education beginning at the family level as an important step in producing a Democratic Germany. R. E.

Your Baby. By GLADYS DENNY SHULTZ, and LEE FORREST HILL, M.D. Pp. 278. Illustrated. Garden City, N. Y.: Doubleday, 1948. Price, $3.50.

"THROUGHOUT these pages we have thought of the father quite as much as of the mother. . . . We should like to emphasize that this book is intended only as a supplement to regular medical care. Spaces are left throughout the book for inserting your own doctor's advice."

NEW EDITIONS

Medical Writing. By MORRIS FISHBEIN, M.D. 2d. ed. Pp. 292; 36 ills. Phila.: Blakiston, 1948. Price, $4.00.

Bailey's Textbook of Histology. Revised by PHILIP E. SMITH, Ph.D., and WILFRED M. COPENHAVER, Ph.D. 12th ed. Pp. 781; 455 ills., many in color. Balt.: Williams & Wilkins, 1948. Price, $7.00.

THE REVISERS continue to aim at a text "primarily for the use of first year students in medicine and dentistry", including physiological significances and more bridges of the gap between gross and microscopic anatomy.

A Textbook of Histology. By ALEXANDER A. MAXIMOW, late Prof. of Anatomy, Univ. of Chicago, and WILLIAM BLOOM, Prof. of Anatomy. 5th ed. Pp. 700; 562 ills., 32 in color. Phila.: W. B. Saunders, 1948. Price, $8.50.

A Method of Anatomy. By J. C. BOILEAU GRANT, M.C., M.B., Ch.B., F.R.C.S. (Edin.) Prof. of Anatomy, Univ. of Toronto. 4th ed. Pp. 852; 799 ills. Balt.: Williams & Wilkins, 1948. Price, $7.00.

A Method of Anatomy has proved its value through 3 previous editions, the first one appearing in 1937. This edition has been improved in a number of ways, most notably by the addition of 68 new illustrations. Professor Grant's book differs from the more commonly known textbooks of anatomy by treating the subject regionally rather than systemically. When used in conjunction with his *Atlas of Anatomy* it provides the first year medical student with exceptionally good instructions for his work. There are many descriptions throughout the book that will be of interest to anyone seeking to recall his knowledge of the structure of the human body. W. W.

Clinical Roentgenology of the Digestive Tract. By MAURICE FELDMAN, M.D., Asst. Prof. of Gastroenterology, Univ. of Maryland. 3d ed. Pp. 901; 641 ills. Balt.: Williams & Wilkins, 1948. Price, $8.00.

THIS book attempts to cover all those aspects of gastrointestinal disease that are of interest to the roentgenologist. It includes, therefore, data on the incidence, the etiology and the symptomatology as well as the roentgen diagnosis of digestive tract lesions. Only their treatment is omitted. Consequently, though a large volume, it presents the individual subjects merely in outline. At the same time the illustrations are excellent and many references are given. The student, whether interested primarily in gastroenterology or radiology, will profit by reading it and by having it available for reference. T. M.

Cancer Manual. Edited by A. W. ERSKINE, S. F. SINGER, D. F. WARD. Cancer Committee of the Iowa State Medical

Society. 2d ed. Pp. 160. Iowa City, Iowa: Athens Press, 1948. Price, $1.00.

THIS work is a concise manual, presenting the essential clinical facts about cancer, and brought thoroughly up to date. It is devoted primarily to symptomatology and methods of diagnosis of the more common malignant growths. Emphasis throughout is on early diagnosis

The treatment of some subjects is confusing and at times only one aspect of highly controversial points is given mention. The section on cancer of the breast suffers from both these faults. These criticisms should not detract greatly from the value of a compendium designed primarily to keep the general practitioner alert to the diagnosis of cancer. However, it does seem that the importance of biopsy might be more generally stressed—indeed, it is stated to be rarely necessary in cancer of the rectum.

R. H.

The Therapy of the Neuroses and Psychoses. By SAMUEL HENRY KRAINES, M.D., Asst. Clinical Prof. in Psychiatry, Univ. of Illinois, College of Medicine. 3d ed. Pp. 642. Phila.: Lea & Febiger, 1948. Price, $6.50.

THE 3d edition, like the preceding editions of this book, approaches Psychiatry mainly from a psychobiological rather than a psychoanalytic viewpoint. It contains new sections on psychiatric geriatrics, pre-frontal lobotomy, group psychotherapy, treatment of epilepsy, a revised classification of psychiatric disorders, and statistical tables on mental disease. W. P.

Manual of Urology. By R. M. LECOMTE, M.D., F.A.C.S., Georgetown University. 4th ed. Pp. 311; 57 ills. Balt.: Williams & Wilkins, 1948. Price, $4.00.

"No attempt has been made to alter the original purpose of the book—to present briefly and simply the underlying principles in urology without complicating discussions, case histories and numerous references."

Handbook of Orthopaedic Surgery. By ALFRED RIVES SHANDS, JR., M.D., with RICHARD BEVERLY RANEY, M.D. 3d ed. Pp. 574; 159 ills. St. Louis: C. V. Mosby, 1948. Price, $6.00.

THIS new edition continues the high excellence of previous editions. The author has carefully revised it, adding new and worthwhile developments in orthopaedic surgery. The introduction of a few Roentgen ray photographs replacing some of the many pen and ink sketches in previous editions is thought to add clarity to the text and make the book more valuable to the student. The author is to be congratulated on bringing this book up to date as a teaching manual and a reference book for the advanced student.

P. C.

Zinsser's Textbook of Bacteriology. Revised by DAVID T. SMITH, M.D., DONALD S. MARTIN, M.D., M.P.H., NORMAN F. CONANT, Ph.D., JOSEPH W. BEARD, M.D., GRANT TAYLOR, M.D., HENRY I. KOHN, Ph.D., M.D., and MARY A. POSTON, M.A., Duke University School of Medicine. 9th ed. Pp. 992; 251 ills. New York: Appleton-Century-Crofts, 1948. Price, $10.00

THE basic approach is from the combined viewpoint of the clinician, researcher, and teacher. The arrangement of the chapters remains about as in the 8th edition. However, the text has been brought up to date as well as a section on antibiotics and a chapter on pleuropneumonia-like organisms added. It contains no material on parasitology. H. M.

Microbiology and Pathology. By CHARLES F. CARTER, M.D., Parkland Hospital School of Nursing, Dallas, Texas. 4th ed. Pp. 845; 216 ills.: 25 color plates. St. Louis: C. V. Mosby, 1948. Price, $5.00.

ALL CHAPTERS have been revised, some very extensively, and new material added. Sulfonamide and antibiotic therapies are discussed. Chapters on Approved Methods of Immunization, Hospital Pathologist and His Work, and Defects of Body Development have been included. H. M.

Sterility and Impaired Fertility. By CEDRIC LANE-ROBERTS, C.V.O., M.S., ALBERT SHARMAN, M.D., Ph.D., KENNETH WALKER, M.A., M.B., B. P. WEISNER, D.Sc., Ph.D., and MARY BARTON, M.B., B.S. 2d. ed. Pp. 400; 96 ills. New York and London: Paul B. Hoeber, 1948. Price, $6.50.

Fractures and Dislocations. By EDWIN O. GECKELER, M.D. 4th ed. Pp. 371; 344 ills. Balt.: Williams & Wilkins, 1948. Price, $5.00.

THIS compact small text has grown larger and more complete in each successive edition. The present volume is to be highly recommended, not as an exhaustive book on the large subject of fractures and dislocations, but as the outcome of a careful personal selection of methods of treatment that will assure good functional results. Both the student and general practitioner interested in bone and joint disabilities will find this one of the best small books published.

P. C.

Diseases of the Eye. By SIR JOHN HERBERT PARSONS, Consulting Ophthalmic Surgeon, University College Hospital, etc., and SIR STEWART DUKE-ELDER, Surgeon Oculist to the King, Consulting Ophthalmic Surgeon to the Army and Royal Air Force, Director of Research, The Ophthalmic Institute, University of London, etc. 11th ed. Pp. 732; 368 figs., 21 plates. New York: Macmillan, 1948. Price, $7.00.

THIS is an excellently prepared short text which now includes all the recent advances in ophthalmology. The section on glaucoma is particularly good, as it includes the modern conception of shallow angle and deep angle type which is adopted in very few standard texts.

While the book contains far too much specialized knowledge for the medical student, it should be a useful reference book for the general practitioner and will certainly be of value to the trained opthalmologist, as it represents the opinions of two world authorities. F. A.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

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CORRECTION

In the abstract in the November issue (**216,** 598, 1948) of **Construction of Normal Standards for Cardiac Output in Man** by J. M. Tanner, the root signs were omitted from the formula, which should be:

$$SV\ (ml) = 100\ \sqrt{2\ area\ I + area\ J\ \sqrt{c}}$$